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AMYOTROPHIC MENINGO-MYELITIS

(SPINAL PROGRESSIVE MUSCULAR ATROPHY OF SYPHILITIC ORIGIN).

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INTRODUCTION.

FOR the application of a new name to a group of cases some apology is perhaps necessary, and the justification for the term "amyotrophic meningo-myelitis" is that it is believed to be reasonably descriptive of the pathological process about to be described and at the same time sufficiently concise for ordinary use. The clinical term "progressive muscular atrophy" is a purely general one; it applied originally to all cases of progressive muscular wasting, and without cumbersome qualification it is not capable of further precision; the method of withdrawing group after group from its scope and applying it to the residue has, indeed, resulted in considerable confusion.

The etiology of spinal progressive muscular atrophy in all but a few cases still eludes our cunning. The cases about to be described are

associated with syphilis, and there is a large body of evidence—pathological, clinical, statistical and therapeutic—that in them syphilis is no chance concomitant but the actual cause of the malady. Much of this evidence will reveal itself as this paper proceeds, and it is not felt that any peculiar argument of it here is necessary. Since the association of progressive muscular atrophy with syphilis is best known from the occurrence of massive wasting in tabes, it must be emphasized from the outset that the cases here considered are not tabetic but are uncomplicated cases of progressive muscular atrophy devoid, for the most part, of any of the recognized clinical signs of nervous syphilis. Tabetic cases have been excluded for two reasons: first, because in studying any process it is important to see it in its greatest simplicity and purity, and secondly, because it was desired to draw particular attention to the presence of syphilis behind the simple cases. It is not denied that the muscular wasting in tabetic cases may be brought about by the same process as in the non-tabetic cases, but it is apparent that the presence of tabes introduces important modifying factors, and so the whole question is reserved for future consideration.

My interest in syphilitic progressive muscular atrophies was aroused by the observation that all the cases of a particular type of chronic progressive wasting that I had seen during three or four years were in subjects who had positive Wassermann reactions. The type is the well-known one in which the atrophy is "atonic"—that is to say, with loss of the reflexes of the wasting muscles—is apparently of spinal origin, and is unattended as a rule by any sensory loss. It is known that a few such cases are due to lead poisoning, and doubtless a few are due to other causes, but my experience would indicate that the great majority of them are due to syphilis.[1] On going to the literature I found that this very thesis had been sustained in France since 1903 by Leri [29], [30], [31], [32], [33], [34], [35].

I have endeavoured to discover from pathological examination the process by which syphilis produces its effects in these cases, and then, since clinical signs of nervous syphilis usually fail us, I have analysed a considerable number of case-histories in the hope of finding some clinical features by which the diagnosis of cases of similar pathology may be aided; finally, I have made a note on the results of treatment.

[1] In a series of eight cases of chronic spinal progressive muscular atrophy of the "atonic" type in which the Wassermann reaction has been performed both in the blood and cerebro-spinal fluid, a positive result has been found in seven. In the remaining case the patient had suffered from recurrent iritis, from diplopia and from weakness of bladder-control, and he had an obstinate sore on the dorsum of the left foot which healed while he was having anti-syphilitic treatment. It is possible that this case, too, may have been syphilitic.

History.

The first suggestion in the literature of the causal relation of syphilis to progressive wasting of the muscles is probably that in the Clinical Lectures of Graves, of Dublin, published in 1795 [20]. Graves had a patient, an officer, aged 60, suffering from a muscular atrophy which had begun five years before in the right hand and had gradually spread up over the forearm to the arm. Graves treated him with mercury and the progress of the disease ceased, and so the physician was led to ascribe to some such cases a syphilitic cause. In 1853 Niepce [41] described to the Académie de Médecine in Paris the case of a doctor the nature of whose affliction had been revealed to him by the appearance of syphilitic sores during a course of spa treatment; in this case a very considerable return of power followed the prolonged administration of potassium iodide. In 1879, Hammond [22], having seen a case of progressive muscular wasting arrested by treatment with iodide, described syphilis as one of the causes of progressive muscular atrophy. Gowers [4], in 1886, wrote: "The disease (chronic spinal muscular atrophy) sometimes succeeds syphilis and no other cause may be traceable. . . . That syphilis has some share in the causation of these cases is probable from its relation to other diseases such as tabes."

In the latter half of last century many cases were recorded in which syphilis was mentioned in the histories, but the writers usually saw in its presence nothing more than a coincidence. The beginning of more exact knowledge dates from the publication of a paper by Raymond [44] in 1893. Raymond reported four cases of progressive muscular atrophy in syphilitic subjects, and in one case he had been able to make a microscopical examination of the spinal cord. He saw that there was not merely a degeneration of the anterior horn cells but also a diffuse meningo-myelitis with much arteritis, and he thought that the degeneration of the anterior horn cells was possibly secondary to vascular disease. Ten years later Leri, in a paper read before a congress of neurologists and alienists at Brussels, described six cases with two autopsies. His findings corresponded closely with those of Raymond; what he called a "diffuse vascular meningo-myelitis" was present in both the spinal cords he examined; he established the fact that the disease was not "systemic" but that all the elements of the cord were involved, and he showed that all the findings were consistent with syphilis being the sole cause.

But the importance of Leri's paper goes further than that, because, after a careful study of the literature, he claimed that a particular

clinical type was nearly always syphilitic, and he thus stimulated interest in the subject, especially in his own country; since that time more than forty-five cases have been published, the majority in France, and at least twelve with microscopical examinations of the spinal cord.

Pathology.

I have had the opportunity of studying the central nervous system fully in one case, and of examining a few representative sections of it in a second case

Case 1.—J. S., a draper, aged 46, a patient in the National Hospital, Queen Square, in 1909, and again in 1923, under the care of Dr Aldren Turner.

Clinical History.—At the beginning of 1907 the small muscles of the left hand began to waste; soon the fingers "dropped" and by May of that year all power of extending the fingers and wrist had gone. By that time, also, the right hand had become affected; it too, wasted and the fingers "dropped"; in July, 1908, the right wrist dropped.

When the patient was admitted to the hospital in 1909 there were no abnormal findings except in the hands and forearms. In particular the pupils were normal, the knee-jerks and ankle-jerks present and the plantar reflexes flexor. The small muscles of the hands and the extensors in the forearms were greatly wasted and gave a complete reaction of degeneration; the flexors of the wrists and the long flexors of the fingers were of good size and power; the supinator longus seemed to be intact in both arms. The tendon-jerks of the biceps, triceps and supinator longus were still present.

After his discharge his condition altered little for three or four years, and then the weakness and wasting of the arms continued its advance, the left arm always being the worse. In 1917 his legs began to feel stiff, and from time to time he had impairment of his bladder control. He was able to keep on at his business till 1919, and continued to walk, though with difficulty, up till May, 1922. The upper limbs had meanwhile become almost quite powerless. At the time of his second admission to the hospital in March, 1923, his condition was as follows (notes by Dr. Carmichael): The lower limbs were spastic in flexion and were the site of frequent flexion spasms which caused much discomfort. No abnormal signs were found in the circulatory, respiratory, alimentary or genito-urinary systems. His psychic functions were normal, the optic discs were healthy, the pupils were equal and reacted briskly to light and accommodation, the movements of the eyes, jaw, face, palate and tongue were all normal, there was no sensory loss on the face; there was some nerve deafness of both ears. The hands and forearms seemed to be only skin and bone; the interosseous space formed a sulcus on the back and front of each forearm, and vessels and nerves were palpable under the skin from elbow to wrist. The upper arms were wasted but not to the same degree; the shoulders stood out sharply owing to the atrophy of the deltoids, and the pectoral muscles were wasted, the right more so than the left. With the exception of a little to-and-fro movement at

the right elbow no voluntary movement could be performed at any of the intrinsic joints of the upper limbs; abduction at the shoulder was very weak, adduction of fair power. The right biceps-jerk was still weakly present, the other arm-jerks were all absent. The lower limbs were extremely spastic and were drawn up on the abdomen; clonus was obtainable at the knees and ankles and the plantar reflexes were strongly extensor. The legs were thin but no gross muscular wasting was present. The abdominal reflexes were absent. There was difficulty in commencing micturition and defæcation. The vibration sense was diminished on both legs; otherwise there was no sensory loss.

The blood gave a weakly positive Wassermann reaction; in the cerebro-spinal fluid the Wassermann reaction was more strongly positive, the protein was increased to 0·05 per cent., but the cells were only 2 per c.mm.

The patient admitted having had gonorrhœa when 22 years of age; otherwise he had enjoyed good health until the muscular wasting began; he was not aware of having had syphilis.

Death occurred from broncho-pneumonia on June 6, 1923.

A partial post-mortem examination was made on the same day, the nervous system only being examined. There was no gross abnormality of the brain or spinal cord, the leptomeninges showed a widespread milky opacity but no thickening of the dura was observed. The brain and spinal cord and portions of the musculo-spiral, median and ulnar nerves, and of the left triceps and biceps muscles, were kept for microscopic examination.

After prolonged fixation in 10 per cent. formol-saline pairs of blocks were cut from:—the mid-brain, pons, upper and lower medulla, each of the segments of the cervical and lumbar enlargements of the spinal cord, and the mid-dorsal portion of the cord and from the cerebral cortex in the precentral (arm), occipital and anterior temporal regions. One set of these blocks was put into Weigert's primary mordanting solution and from them, after they had been embedded in celloidin, sections were eventually stained by the Weigert-Pal method. From the other set of blocks, after washing, alcohol-fixation and embedding, sections were obtained which were stained by Nissl's method, or with hæmatoxylin and van Gieson's stain. Portions of muscles were also sectioned and stained by the hæmatoxylin and van Gieson's method. The portions of nerves were unfortunately lost.

Microscopical Examination.

Spinal cord. Cells.—Of the extent of the cellular degeneration in the spinal cord some idea may be formed from the accompanying table, which compares the average number of anterior horn cells found in four sections through each of the segments mentioned, with the normal number as given in Bruce's "Atlas of the Spinal Cord."

In the cervical enlargement there was sometimes not a single cell left in a whole anterior horn and perhaps very few recognizable fragments; anything approximating to a normal cell either in size or appearance has been counted. In the lumbo-sacral enlargement, perhaps half the cells counted contained nuclei.

Segment	Average number of cells present	Normal number	Segment	Average number of cells present	Normal number
C V	17	146	L I	28	92
C VI	7	120	L II	22	100
C VII	4	120	L III	57	128
C VIII, upper part	7	132	L IV	49	188
C VIII, lower part	1·5	118	L V	91	180
D I	8	106†	S I	100	188
Mid-dorsal ..	17	56	S 2	65	130
—	—	—	S 3	17	68

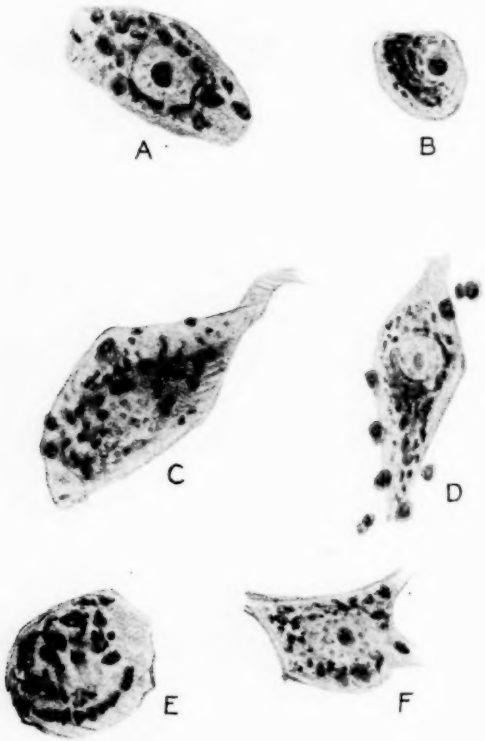

FIG. 1.—*Case* 1. Drawings of representative anterior horn cells from the cervical enlargement.

The Nature of the Cellular Change.

The type of cellular change which prevailed was different in the upper and lower portions of the cord. In the cervical enlargement the earliest stage

seemed to be represented by chromatolysis round the periphery of the cell and a concentration of intensely stained Nissl granules close round the nucleus. Nearly all the cells seen in this stage (e.g., fig. 1, D, F), had already lost their dendrites and had become small (B) and usually oval in form (A); the nucleus

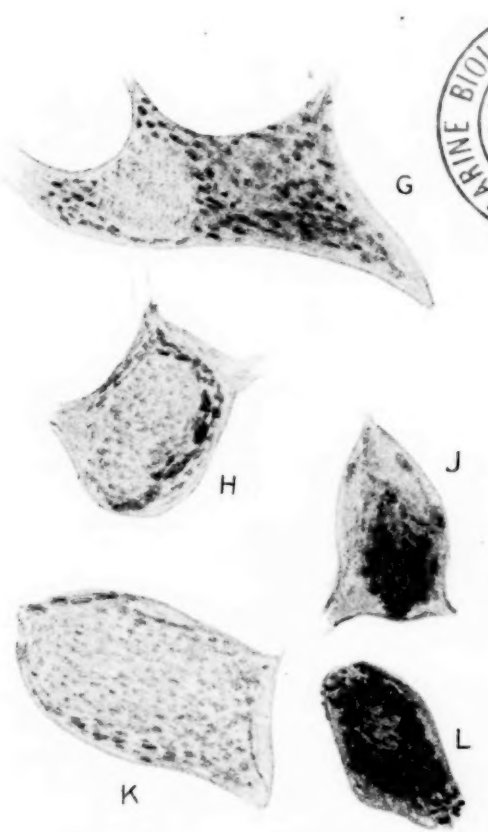

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FIG. 2.—*Case* 1. Drawings of representative anterior horn cells from the lumbar enlargement.

in them was still central. The next stage seemed to be the breaking down of the nuclear membrane (C, E); the Nissl granules, often larger than normal, continued to gravitate towards the centre and occupied the nuclear area, the margin of pallor in the cytoplasm becoming wider and wider. Finally the cell membrane

seemed to break down and a shapeless collection of blue-stained granules, blanching from without inwards, was the last recognizable state of the vanishing cell. In a very few cells the chromatolysis was perinuclear.

Here and there small clumps, five or six, of relatively healthy cells were left when all those around had been completely destroyed; these cells which were spared never appeared quite healthy but showed early stages of the degeneration.

In the lumbar and sacral regions there were very few healthy cells, but only a small proportion of the diseased cells showed the type of degeneration present on the cervical cord.

In the commoner type, while some peripheral chromatolysis was generally visible, the more dominant change seemed to begin around the nucleus. The nucleolus disappeared, the nuclear membrane broke down, and then it was as if the nucleus had melted and slowly flowed out over the cytoplasm, dissolving the Nissl granules as it reached them until the whole cell was of uniform colour; the cytoplasm then had a finely granular or powdery appearance. Two stages of this process are represented in cells H and K (fig. 2). The cells gradually lost their dendrites; they seemed to become paler and paler and disappear, probably in fragments. In numerous other cells, especially in the lumbar cord, the process was a modification of that found in the cervical region; chromatolysis began in a circumscribed area, very definitely demarcated and usually touching the periphery of the cell (see G.); the Nissl granules tended to gather round the nucleus; the nucleus became excentric, the nucleolus and nuclear membrane disappeared, the pale circle enlarged and the Nissl granules were driven to one side or corner of the cell (see J); finally the cell-membrane broke down, leaving, as in the cervical enlargement, a shapeless mass of pigmented granules. No vacuolation of cells was seen.

Tracts.—In Weigert sections (figs. 3, 5 and 6) a very extensive degeneration of the tracts was seen; it affected all the antero-lateral white matter, and in a minor degree the posterior columns. There were several features which distinguished the case at a glance from one of idiopathic amyotrophic lateral sclerosis. The first was the great degeneration round the margin of the sections. From a narrow peripheral area, not definitely demarcated towards the more central part of the cord, usually most marked antero-laterally and least posteriorly, all trace of fibres had disappeared. This marginal degeneration was seen at all levels, but between the fifth cervical and the first lumbar segments it had penetrated more deeply, and in the middle of the cervical enlargement it reached its maximum. It was of sufficient depth to be visible to the naked eye, and destroyed a large fraction of the ascending cerebellar tracts, of the direct pyramidal tract, and at some levels the posterior margin of the columns of Goll and Burdach. The second distinguishing feature was the degeneration in the posterior columns. Throughout the cord this degeneration affected chiefly the columns of Goll, but in sections through the cervical enlargement the whole area of the posterior columns had an uneven pallor which was in striking contrast to the resolute blackness of the same area in the true

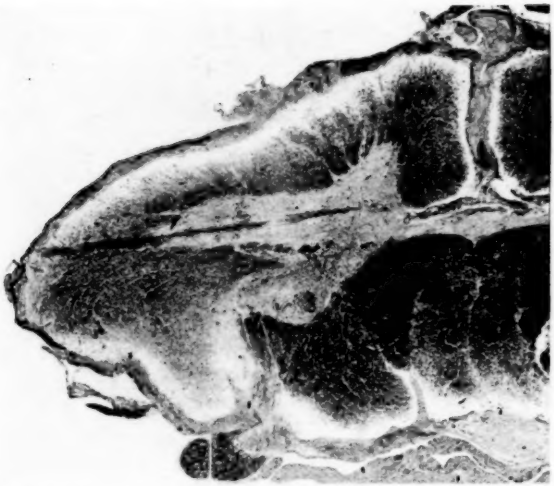

FIG. 3.—*Case* 1. A section through the eighth cervical segment, stained by the Weigert-Pal method, counterstained with eosin. Note: (1) The marginal degeneration; it has destroyed the spino-cerebellar tracts and part of the direct pyramidal tract; (2) the degeneration in the columns of Goll; (3) the diffuse degeneration of the antero-lateral white matter. Compare with fig. 4.

FIG. 4.—A section from a case of idiopathic amyotrophic lateral sclerosis for comparison with fig. 3. There is no marginal degeneration and the cerebellar tracts are spared, the posterior columns are intact; the tract degeneration affects the pyramidal tract most severely.

Charcot's disease (figs. 3 and 4). The degeneration in the columns of Goll as it appeared in the cervical enlargement had not the intensity nor the distribution of the posterior column degeneration of tabes; it was in all probability due to the marginal degeneration of the posterior surface of the cord down in the lumbar region. Again, in all segments of the cord down to the third lumbar

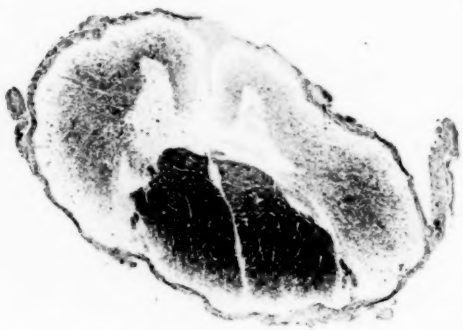

FIG. 5.—*Case* 1. A section through the mid-dorsal portion of the cord, stained by the Weigert-Pal method, counterstained with eosin.

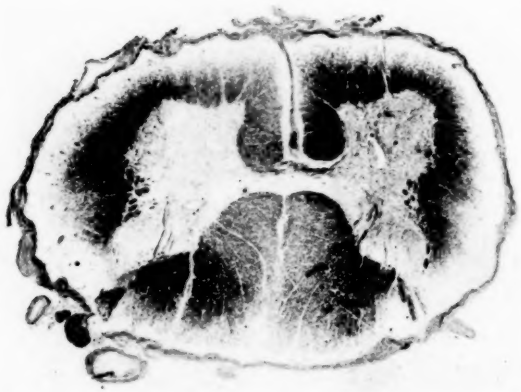

FIG. 6.—*Case* 1. A section through the second lumbar segment, stained in the same way as fig. 5.

the fine fibres in the grey matter had suffered very great destruction; in the lower part of the cervical enlargement they were almost entirely absent. In the commoner disease this fine fibre network is relatively well retained.

The pyramidal tracts presented considerable degeneration throughout their whole length, but it was more severe from the fifth cervical segment down-

wards. The two sides were not affected equally. The fact that the direct pyramidal tracts were also severely degenerated might at first suggest that the pyramidal pallor was due to disease affecting the pyramidal paths above their decussation. But closer examination shows that the degeneration of the direct pyramidal tracts was much more intense than that of the crossed, and that in the cervical enlargement it was part of the degeneration of the margin of the cord. It was therefore probably independent of the degeneration of the crossed tracts. Degeneration of the pyramidal path extended right up to the mid-brain, but I am inclined to think that the superior degeneration was retrograde and that the degeneration of the crossed tracts was due, if not wholly, then at least in great part, to disease in the cervical enlargement.

Medulla.—In the medulla there was considerable cellular degeneration. In the twelfth nerve nuclei only seven out of thirty-three cells in the right and sixteen out of forty-eight cells in the left were healthy; in the tenth and eleventh nerve nuclei of the right side there was a large number of unhealthy cells, but in those of the left only a moderate amount of chromatolysis in their more anterior cells. In one section not one of the nineteen cells seen in the right nucleus solitarius was healthy and only two or three of the fifteen cells seen in the left. In the substantia gelatinosa Rolandi in the same section there were no healthy cells on either side, all showed some chromatolysis; in the anterior part of the substance the cells were shrunken and many had lost their nuclei, and in the posterior part the cells were large and swollen.

In Weigert sections considerable degeneration was seen in both pyramids, but less on the left than on the right. The degeneration of the cerebellar tracts was extreme. The fillets were somewhat pale.

Pons and mid-brain.—No pronounced cellular degeneration was observed.

Cerebral cortex.—In the cortex of the frontal, occipital and temporal regions the cellular appearances were normal. Over all these areas the lepto-meninges were moderately thickened and showed considerable infiltration with lymphocytes; the small arteries within the brain tissue were similarly infiltrated.

Over the cortex of the left motor (arm) area the amount of meningeal and perivascular infiltration was less than in the other regions. The cortical motor cells showed some slight changes; in occasional cells the nucleus lay at the surface and a few were paler than the normal. It is possible that there was some reduction in the number of the large motor cells, but this cannot be definitely asserted, and none of these cells was seen in advanced stages of degeneration.

The glial reaction.—The glial reaction was examined in sections stained by Anderson's methyl-violet method and by van Gieson's stain. The place of the degenerated grey matter was, as might be expected, taken up by glia; under a very low power relatively pale circumscribed areas could be picked in these glia-stained sections, and it was found that in these areas ganglion cells persisted. Small glia nuclei were very numerous and there were a great many (10 to 20 per cent.) larger nuclei. All this mass of glia, and in fact the whole cord in the

cervical region, was infiltrated with small cells which could not be distinguished from the lymphocytes in the meninges and which were regarded as lymphocytes.

In the degenerated margin of the cord the glia was not increased. There were few nuclei except close to places where the pia was adherent to the cord, and here they were accompanied by a large number of lymphocytes within the nervous tissue.

In the medulla there were little masses of glia in the leptomeninges or on their outer surface (fig. 7); they were always at or close to adhesions of the pia to the surface of the brain-stem; below the medulla they were not found with certainty, for no mass near the entrance or exit of nerve roots was counted. The glia in these masses had a fairly dense meshwork, and both small and

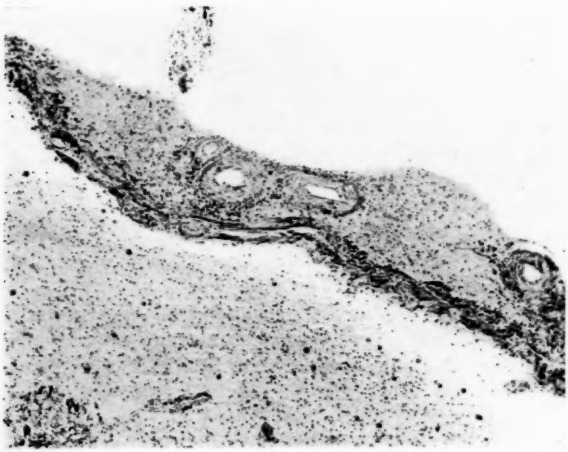

FIG. 7.— *Case* 1. Small masses of neuroglia on the outer surface of the lepto-meninges of the medulla.

large nuclei were present in large numbers. In several places the continuity of the fibres and of the groups of nuclei with those within the cord could be seen at the points of meningeal adhesion.

In van Gieson sections the colour of the glial masses contrasted with that of the meninges.

Perhaps the most remarkable reaction was on the ependymal surface of the brain-stem. The fourth ventricle and the iter of Sylvius were partly filled up with an elongated mass (see fig. 8) composed partly of proliferated ependyma and partly of glia. In van Gieson sections it took the yellow colour of glia, and in sections stained by the methyl-violet method it was found to be composed of rather coarse glia fibres. These latter formed a network of very variable intensity, but however loosely they interlaced at places within the

mass, they usually formed a dense texture at the ventricular surface. Among the fibres were swarms of cells of which presumably the nuclei only were stained. In the most dense fibre network they were as a rule fewer and were small and round, at any rate towards the surface. The shape of the nuclei and the arrangement at other parts depended on the surrounding conditions; within a regular meshwork they were round or slightly oval and irregularly scattered, but among numerous dense fibres running mostly in one direction they were more elongated and arranged at intervals along lines between the fibres. At places they were apparently continuous with fibres, and sometimes there were

FIG. 8.—*Case* 1. Neuroglial outgrowth in the fourth ventricle. Note the thickening of the ependyma and the irregularity of its outline.

seen spindle-shaped widenings on the fibres with nuclear appearances and pigmentation.

The ependymal cells were arranged within this mass with much irregularity, but seldom far from their original plane, so that, for instance, the outline of the calamus scriptorius could still be seen (see fig. 8). There was a great overgrowth of them at all levels, perhaps best seen, because most confined, in the iter of Sylvius. They differed from the other cells of the mass in that they were slightly rounder, larger (fatter) and not quite so deeply stained, and especially in that they arranged themselves in continuous rows in straight lines or irregular circles. In some places the great numbers of minute circles formed by these cells produced an appearance resembling a section of an adenoma. The cells of this proliferating ependyma were considerably smaller than the normal ependymal cells in the fourth ventricle. Under the ependyma, i.e., in

the nervous tissue of the floor of the fourth ventricle, the small blood-vessels were dilated and distinctly increased in number.

Vessels.—Within the spinal cord the capillaries and arterioles were in many places very numerous (van Gieson sections). The arterioles had numerous cells lying along them (lymphocytes, and a few compound granular corpuscles). The small arteries had their intimal and adventitial coats greatly thickened (see fig. 9), and within the adventitia numerous lymphocytes lay. Except where the lymphocytes were exceptionally numerous they did not occupy the Virchow-Robin space. The perivascular lymphocytes were perhaps rather more dense in the lumbar portion of the cord than in the cervical. No thrombosed or obliterated vessels were seen.

Meninges.—The leptomeninges were much thickened, and all over the cord and brain-stem frequently adherent to the nervous tissue. The pial fibres had

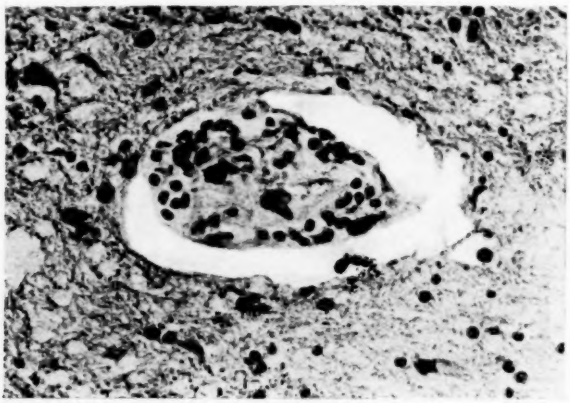

FIG. 9.—*Case* 1. A small artery in the spinal cord, showing thickening of the intimal and adventitial coats, and numerous lymphocytes lying between the laminæ of the adventitia.

to a great extent lost their usual tangential arrangement and formed a much more irregular texture than in the normal. Everywhere the meninges were infiltrated with cells—practically all lymphocytes, but there were a few plasma cells (one in about every second high-power field). The small glial masses on the meninges of the brain-stem presented a similar lymphocytic infiltration. The intimal and adventitial coats of the vessels of the meninges were greatly thickened, even as contrasted with the vessels within the cord.

Muscle.—Sections from the left biceps and triceps showed in a very severe degree the type of degeneration that ensues in muscles deprived of their nerve-supply. A few bundles of healthy-looking striated fibres remained, but in the majority there was no vestige of a muscle fibre, but only swarms of sarcolemmal nuclei; between the bundles there was an excess of fibrous tissue. A muscle spindle was seen in one of the sections and appeared quite healthy.

Summary of the Pathological Findings.

The pathological findings, in short, were :—

(1) A chronic leptomeningitis throughout the whole length of the cord and medulla.

(2) A severe ependymitis.

(3) An intense glial reaction towards both surfaces of the brain-stem.

(4) Intense degeneration of the white matter round the margin of the cord.

(5) A less degree of degeneration of the more central white matter, the columns of Burdach being the least affected ; this tract degeneration was most pronounced in the middle of the cervical enlargement.

(6) Degeneration of the anterior horn cells and of the cells of Clarke's column, almost absolute in the cervical enlargement, much less, but still very definite, throughout the remainder of the cord. The type of cell degeneration in the cervical enlargement appeared to be different from the type which predominated in the lower portions.

(7) A moderate degree of arteritis, affecting chiefly the intimal and adventitial coats of the vessels ; the small vessels within the cord were increased in number. Throughout the cord and meninges there was a moderate amount of perivascular infiltration with lymphocytes.

There is every indication that the whole process was syphilitic ; the meningitis was typically so, the arteritis almost characteristic, the degeneration in the posterior columns was very suggestive of syphilis, similar marginal degeneration of the cord has been described time and again in syphilitic cases (" syphilitic halo "), the granulomatous appearance on the ependymal surface of the medulla is seen in some cases of tabes, and the type of cellular degeneration found here in the cervical enlargement has been described and illustrated minutely by Lapinsky [8] and others in tabes, and by Berger [2] in general paralysis of the insane.

Through the kindness of Dr. R. T. Williamson I have had the privilege of examining some sections of a case clinically similar to that just described, which was published by him in 1901.

Case 2.—The case was that of a Frenchman who for many years had sold matches in the streets of Manchester. He suffered from a slowly progressive atrophic paralysis which had begun in the hands and gradually spread up over his arms to the muscles of the shoulder-girdle and finally of the neck. For twenty years before his death his arms had hung helpless by his sides and his head was bent forwards. At the last examination, twelve months before his

death, all the muscles of the arms were powerless and atrophied, the arm-jerks were all absent, but sensation was unimpaired; the lower limbs were quite normal, their muscles were of good power, the knee-jerks and ankle-jerks were

FIG. 10.—*Case* 2. A section from the upper cervical portion of the cord, stained by Weigert's method. Note the marginal degeneration, the degeneration in the columns of Goll and the thickened lepto-meninges.

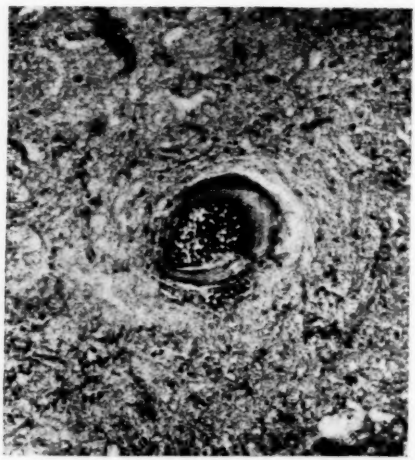

FIG. 11.—*Case* 2. A small artery in the spinal cord, showing great (hyaline) thickening of its wall and a cluster of lymphocytes lying in the Virchow-Robin space.

present and equal on the two limbs, and there was no ataxia, no sphincter trouble and no signs of bulbar paralysis.

Clinically his case corresponded to the pre-spastic stage of Case 1.

Microscopical examination.—In a section through the eighth cervical segment not a single anterior horn cell could be found. The anterior horns are shrunken and the glia in them is enormously increased. The Weigert sections of other segments reveal marginal degeneration (fig. 10) and some degeneration in the column of Goll; on one side the pyramidal tract is intact, on the other side it shows a very little degeneration. The fine fibres in the grey matter have undergone the most extreme destruction. The leptomeninges are greatly thickened and adhere to the surface of the cord (fig. 10). The arteries of the cord and meninges have greatly thickened walls, with a perivascular infiltration with lymphocytes (see fig. 11).

In short this case has all the essential pathological features of Case 1, and differs from it chiefly in that the tract degeneration is less severe. The state of the meninges and the marginal degeneration of the cord are indicative of syphilis, and the condition of the arteries, though not typical, offers some supporting evidence to the same effect. There can be little doubt that the process at work in the two cases was the same.

Observations on the Pathological Features.

Similar findings in cases of progressive muscular atrophy without any clinical manifestations of nervous syphilis have been recorded by Oppenheim [43], Dreschfeld [18], Raymond [44], Strumpell [52], Leri et Lerouge [34] (two cases), Braun [15], Medea [38], Merle [39], Sainton [47], Lannois et Perot [28], Alquier et Touchard [14], Leopold [36] and others. In all the later cases the condition has been recognized as being of syphilitic origin and in some of the earlier ones the subjects are known to have had syphilis. Cases pathologically similar, but in which Argyll Robertson pupils were present to aid the clinical diagnosis, have been published by Spiller [51] (two cases), Dana [17] and others.

For further consideration we may divide the pathological findings in all these cases into two parts—on the one hand the meningitis and the marginal degeneration of the cord, on the other the cellular destruction in the grey matter and the diffuse tract degeneration. These two groups of changes are never completely dissociated, but they do show some degree of independent variation.

Dr. Williamson's case (Case 2 above) represents the minimum of marginal and tract degeneration for the amount of cellular destruction. In my Case 1 and in the cases of Merle [39], and of Lannois and Perot [28], which resemble it very closely, a more even balance is maintained between the two portions of the picture. In the case of Alquier and

Touchard [14], while the cellular destruction was severe, the marginal degeneration predominated; it had bitten so deeply into the cord that it reached the spino-thalamic tract and was partly responsible for a dissociated anæsthesia of irregular distribution which the subject had exhibited during life. Finally, there are the cases described by Raymond and Cestan [11] under the title "Méningo-myélite marginale progressive," in which the cellular destruction took a minor place and the marginal degeneration was the chief pathological change; clinically these were cases of spastic paraplegia and slight muscular wasting in syphilitic subjects.

In nearly all cases the site of maximum cellular destruction has been in the cervical enlargement, and in almost all it has been of a severity quite comparable to that described in Case 1. A few patches of relatively healthy cells lying in areas otherwise denuded are mentioned in many descriptions. In Sainton's [47] case the chief damage was in the lumbo-sacral region; this case is of particular interest because it was thought to be one of Charcot-Marie-Tooth atrophy, but the disease came on rapidly in middle life in a subject known to be syphilitic and the pathological findings were similar to these I have described.

The meningeal change shows little variation from case to case, and my Case 1 may be taken as typical in this respect; the number of lymphocytes present in the meninges indicates an inflammation that is almost subacute. But the amount of ependymal change and the glial outgrowths on the brain-stem which were found in Case 1 are very unusual; some degree of ependymal thickening is common, but I have not found any description of a proliferation to the extent that was seen in my case, nor of the epi-ependymal outgrowth of glia. The glial outgrowths on the ependymal and pial surfaces of the brain-stem were both presumably due to the same process, and are of the same nature as the small glial masses which are seen in the ependyma in some cases of general paralysis and of tabes. The proliferation of the ependyma, the numerical increase and the dilatation of the blood-vessels beneath the ependyma, and the infiltration of the floor of the fourth ventricle, and of the pia, the neighbouring margin of the cord and the glial masses themselves with lymphocytes, all go to show that these ventricular and meningeal outgrowths of glia were part of an inflammatory reaction; and since the noxious agent by which that reaction was called forth was syphilis, it is probable that they are true granulomata.

The glial overgrowth within the degenerated cord is less remarkable, but one point concerning it is worthy of note, that is the possibility that

it may break down and so lead to the formation of syringo-myeloid cavities; such necrosis had occurred in the case of Alquier and Touchard [14] to which I have already referred, small cavities being present in the upper cervical cord and the medulla.

Finally, some variation is found from case to case in the state of the vessels. In practically all the reported cases which really belong to the class under discussion, there has been a pronounced endo- and peri-arteritis in the cord and in the meninges, but whereas in some cases the vessels have been thickly surrounded with lymphocytes, in others (e.g., Merle's case) it has only been with difficulty that any perivascular infiltration could be discovered, while in some cases of an associated nature (e.g., Holmes [26], Spiller [51], Wilson [56]), no definite vascular "cuffing" has been observed. Now in Case 1 the infiltration of the adventitia of the arteries was everywhere definite, but the lymphocytes hardly ever extended to the Virchow-Robin space; the appearance made one think of the hypothesis which Bertrand has put forward to explain perivascular lymphocytic infiltration in other diseases, viz., that the adventitia of the vessels in an area permeated with toxic substances, reacts by undergoing a "lymphoid metaplasia" and itself produces the lymphocytes which are seen between its layers and in the surrounding space. On such an hypothesis it is natural to think that the capacity of the vessel wall for lymphocytic reaction must vary somewhat according to its antecedent condition and an explanation of the differences that have been observed is thus afforded. Leri considers that the perivascular infiltration decreases as the disease becomes older and less active, but, though that is probably true, it fails to account for the scantiness of the infiltration in certain cases in which muscular wasting was still progressing at the time of death.

But whichever view be taken, the state of the vessels is additional evidence that we are dealing with an inflammatory condition; we have all the elements of a diffuse meningo-myelitis, and since one of the outstanding features of it is degeneration of the anterior horn cells it merits the designation "amyotrophic meningo-myelitis."

Pathogenesis.

Now if all these changes are syphilitic, in what way does syphilis produce such effects? Several circumstances suggest that the destructive influence reaches the nervous tissues mainly by diffusion and infiltration from the surface of the cord and brain-stem. The marginal degeneration of the white matter of the cord and the glial reaction on the surface of

the medulla are particularly significant in this regard. In the next section it will be shown, too, that the wasting in the majority of cases begins in the small muscles of the hands, that is in those muscles which are represented in the outermost parts of the cervical anterior horns and next attacks the extensors of the wrist and fingers, which have the next outermost representation [13].

It may therefore be surmised that the first stage of the process is an infection of the leptomeninges with syphilitic organisms. In consequence of the resulting inflammation the matted arachnoid and pia become adherent to the cord, and the physiological moat having thus been bridged, toxins from the meninges probably invade the outlying margin of the cord and destroy it fibre by fibre. It will be shown later that the Wassermann reaction in the cerebrospinal fluid in many cases quickly becomes negative when antisyphilitic treatment is given, and from this fact alone it is probable that the site of the infection is in the meninges and not in the nervous parenchyma.

Again, the cellular destruction and the marginal degeneration show great relative quantitative variation from case to case; it is therefore likely that the former is brought about in a somewhat different way from that just suggested for the latter. It may, of course, be that the whole cord is permeated *per continuitatem* by toxins from its surface, but this explanation does not seem adequate for Case 2 (Dr. Williamson's) and cases like it, in which the white matter between the margin and the degenerated cells has apparently not suffered, neither does it explain the relative escape of the posterior columns in all cases. Some subsidiary explanation is required.

Another hypothesis, and the one which has been most favoured, is that the destructive influence, whatever it be, is directly associated with the vascular disease. Now, in my Case 1 and in most other cases recorded, the changes in the vessels were not of sufficient severity to kill the cells and tracts by deprivation; nor in the less affected portions of the cord in Case 1 could any relation of cellular damage to particular vessels be made out. If, instead, we suppose that the part of the vessels in the destructive process is the transmission of a toxic substance into the central nervous tissues from the blood, we encounter the same objections as have already been set against total permeation of the cord from its surface. Moreover, it will be shown later that the Wassermann reaction in the blood is negative in about one-third of all the cases. While, therefore, vascular disease is usually present and must have an adverse influence on the well-being of the nervous elements, it cannot be held wholly accountable for their death.

Lastly, it is possible that the syphilitic toxin, to reach the central parts of the cord, makes use of the lymph channels. This is by far the most satisfying hypothesis, for it explains the sparing of the posterior columns. They are known to have a lymph system separate from that of the remainder of the cord; they may therefore escape when the rest of the cord is affected from the lymph-stream, or, conversely, they may be affected alone. In the latter case the disease would resemble tabes dorsalis and would not come within the scope of this paper, while in the former the degeneration would be produced in the antero-lateral white matter and in the grey matter just as in the cases under discussion.

Whatever explanation be adopted, it must be assumed that the cell bodies in the grey matter are more easily overcome than the tracts of the white matter. That this would be the case is to be expected from their lack of a myelin covering and from the analogy of diseases such as acute anterior poliomyelitis.

Other suggestions that have been put forward to explain the cellular degeneration are that it may be the result of disease of the peripheral nerves or anterior roots, or of the isolation of the cells by the interruption of the reflex and pyramidal paths. With so much other destruction within the cord it seems unnecessary to look outside it for the source of the cellular change, and in any case the type of the cell degeneration is not that which results from a *réaction à distance*. The hypothesis of isolation is insufficient because it is inapplicable to those parts of the cord where the degeneration is not advanced (e.g., the lumbar region in Case 1), and few of the writers who have considered it have regarded it as at all adequate.

General Clinical Features.

Since in amyotrophic syphilitic meningo-myelitis the generally accepted clinical signs of nervous syphilis usually fail us, we must endeavour to find out whether there are other clinical features by which we can diagnose these cases from other kinds of progressive muscular wasting, or by which our suspicions may at any rate be aroused. The following analysis is based on the histories of recorded cases in which the diagnosis has been confirmed by microscopical post-mortem examination; there are, however, numerous cases from one's own experience or from the literature, in which the patients are still alive, which correspond so closely with the others that the diagnosis admits of little doubt; to neglect this large material, with its possibilities for

showing the minor deviations from the main lines of the disease's progress, would be foolish, and so I have made use of some sixty cases in all, seven of them being from my personal experience.

In the description that follows, I shall avoid using Charcot's division of cases into "amyotrophic lateral sclerosis" and "progressive muscular atrophy," for in dealing with an entity in which the amount of tract degeneration is variable, it is necessary to use terms which shall be applicable to a case from its inception to its termination, whether spasticity occurs or not.

Period after infection.—The average period between the syphilitic infection and the onset of wasting in those cases in which it could be ascertained, was seventeen years, with extremes of four and thirty-seven years. A few cases have been recorded in the subjects of hereditary syphilis (Nonne).

Age and sex.—The great majority of the patients are males—50 males and 10 females in the 60 cases. The ages vary from 29 to 75 years, with an average of 48; two-thirds of the cases (39 out of 60) begin between the ages of 34 and 50.

Illustrative Cases.

(a) With the wasting beginning in the hands.

Case 1 (p. 156).

Case 2 (Dr. Williamson's) (p. 167).

Case 3.—E. S., female, aged 50, married; admitted to the National Hospital under the care of Dr. Aldren Turner in June, 1922, discharged six weeks later: subsequently under the care of Dr. Kinnier Wilson as an out-patient. No history of syphilis. No children, one miscarriage. Four years before admission she had noticed weakness of the left wrist; she thinks left hand was even then thinner than right. Soon she became unable to lift objects with the left hand. A year before admission she felt dizzy for several days, during which time the left hand became worse; afterwards she had difficulty in putting it to the back of her head when doing up her hair. On clinical examination the cranial nerve functions, including pupillary action, were all normal; the right arm and both the lower limbs were normal, the gait was normal and Romberg's sign absent, the knee-jerks were brisk, the ankle-jerks normal and the plantar reflexes flexor. In the left hand all the intrinsic muscles were greatly wasted and were powerless; in the left forearm the extensors and flexors of the wrist and fingers were wasted and weak, the extensors being much weaker than the flexors; the grip was feeble. In the arm the biceps and triceps were both somewhat wasted and the deltoid much more so; flexion and extension at the elbow were not strong, but abduction at the shoulder was so weak that the arm could not be raised by voluntary action within 30 degrees of the horizontal. The pectoral

and scapular muscles were of good bulk and power. The tendon-jerks of the left arm were all absent, those of the right arm were normal. The Wassermann reaction was positive in the blood, but negative in the cerebrospinal fluid; the fluid contained six lymphocytes per cubic millimetre and 0·03 per cent. protein. The patient had been treated with iodide and mercury before her admission, in hospital she received in addition injections of novarsenobillon. The wasting muscles were treated with massage and faradism. In the two and a half years since this treatment was given the disease has made no advance.

(*b*) *With the wasting beginning in the shoulder-muscles.*

Case 4.—W. H., aged 54, wheelwright, under my care at Maida Vale Hospital. In September, 1924, he came complaining of severe pain of two months duration in the left shoulder and upper arm. He suffers from long-standing deafness of obstructive origin. Examination showed extensive corneal opacities, the pupils were slightly unequal, but reacted well to light and accommodation. The breathing was accompanied by stridor suggestive of abductor paralysis of the vocal cords, but no such paralysis was present. All movements at the left shoulder were weak and the arm could not be raised voluntarily to the horizontal; there was some wasting and brisk fibrillation in the left deltoid, biceps, triceps and pectoralis major; the extensors of the wrist were slightly but definitely weak; the left hand was normal. The tendon reflexes were absent in the left arm, elsewhere present and normal; the plantar reflexes were flexor; there was no sphincter trouble and no sensory loss. The right arm and lower limbs were normal. The Wassermann reaction was positive in the blood. The cerebrospinal fluid was not examined until the patient came into hospital several weeks after treatment had begun; it then gave a negative Wassermann reaction, but contained 42 lymphocytes to the cubic millimetre. Since the first few weeks of treatment there has been no advance in the paralysis and the fibrillation has almost ceased; the pupils have become equal and the corneal opacities have completely cleared.

Case 5.—T. G., aged 43, pensioner, admitted to the National Hospital in December, 1920, under the care of Dr. Buzzard; subsequently under the care of Dr. S. A. K. Wilson and other physicians. In October, 1916, he had aching pains in both shoulders and in the back of the neck, and a month later he noticed a diminution in the power of his arms; this weakness progressed and was accompanied by a wasting of the arms from the shoulders to the elbows. He felt slight weakness of both legs. There was no bladder trouble. When he was admitted to hospital the pupils were unequal, but were regular in shape and reacted normally; the cranial nerve functions were otherwise normal. In both arms there was great wasting of the deltoids, supraspinati, biceps and triceps; the infraspinati were slightly wasted, the pectoral muscles were of good size and power; supination was weak in both arms, no weakness or wasting was found in the hands. Fibrillation was present in the spinal muscles of the upper dorsal region. The lower limbs were slightly spastic, the knee and ankle jerks being increased, the left plantar reflex extensor and

the right indefinite. The abdominal reflexes were present. There was no sphincter trouble. The gait was normal. There was no sensory disturbance. The spine showed a little curvature with the convexity to the right. The Wassermann reaction was negative in the blood and positive in the cerebrospinal fluid; the latter contained eight cells to the cubic millimetre. The disease made no progress in the sixteen months that the patient was under observation during and after his period of treatment.

(c) *With the wasting beginning in the legs.*

Case 6.—F. D., aged 58, carriage cleaner, under my care at Maida Vale Hospital. He was healthy till the summer of 1921; then he began to feel his legs weak; his legs got rapidly weaker and thinner and within twelve months he was unable to walk. When he was examined at the hospital in June, 1922 (Dr. Riddoch), he had great wasting of all the muscles below the knee in both lower limbs; there was bilateral foot-drop and practically no power of movement at either ankle. The ankle-jerks were absent, the plantar reflexes unobtainable; elsewhere the reflexes were normal. Vibration sense was lost in the legs but there was no other sensory loss. The pupils were normal. The Wassermann reaction was negative in the blood, but positive in the cerebrospinal fluid. After a course of antisyphilitic treatment the Wassermann reaction became negative in the cerebrospinal fluid, and the disease has made no progress since the treatment was given.

Mode of onset.—In the majority of cases (77 per cent.) the first symptom complained of was weakness, but as some wasting appears to have been discovered at the first examination in all these cases, there is no reason to believe that any weakness preceded the atrophy.

In 23 per cent. of cases (fourteen out of sixty) the first symptom was pain. This was in most cases a constant severe pain of several weeks' duration, often referred to the shoulder or half of the back of the neck on the side on which the wasting later appeared. In two cases lightning pains in one arm preceded wasting in that limb. I have not found any case which began with spasticity, but it is to be expected that some cases would begin in this manner (see the cases of Raymond and Cestan [11]).

Wasting.—An overwhelming majority of the cases show the "atonic" type of atrophy—atrophy with loss of reflexes in the wasting muscles. Of thirty-nine cases in which the state of the tendon-jerks of the wasting muscles is recorded, it is stated in thirty-one that they were absent, in six that they were decreased, in one that they were normal and in one that they were increased.

The wasting nearly always (93 per cent. of cases) began in one of three situations—the small muscles of the hand, the shoulder-muscles,

or the muscles on the outer side of the leg. In three-fifths of the cases it began in the small muscles of the hand. It was usually noticed first in the thenar eminence and the power of adduction and apposition of the thumb were lost; at the same time the interosseous spaces became hollow. Soon weakness was felt, not as one might expect in the flexor, but usually in the extensor group in the forearm. At this stage a typical case (see above) shows fibrillation in the extensors and generally loss of the supinator jerk; in a few cases the supinator longus muscle (with its higher segmental supply) has been relatively spared and has for a time retained its tendon-jerk. As the extensors waste the wrist drops and the fingers become flexed at their intrinsic joints. The flexors then become affected, but they do not often lose their power with the same rapidity as the extensors. Subsequently fibrillation and weakness may begin in the biceps and triceps, but more characteristically these muscles are spared for a time and the disease jumps from the forearm to the deltoid, and it is only after the deltoid and perhaps the scapular and pectoral muscles are considerably wasted, that the biceps and triceps finally atrophy. These "jumps," though they do not occur in all cases, are very characteristic of the disease: they are to be associated first with the fact that the degeneration within the cord probably spreads from without inwards more than from segment to segment, and secondly with a certain "patchiness" which is apparent in the cellular destruction in the spinal cord.

Both upper limbs may be affected simultaneously and the wasting progresses then *pari passu*. But one limb may be entirely withered and its fellow remain intact (see Case 3).

In 22 per cent. of cases the wasting began in the shoulder-muscles. The deltoid, the supra- and infra-spinati and the upper part of the pectoralis major, all supplied from the same segment, usually become affected in quick succession. Wasting of the rhomboid and trapezius and of the muscles of the back of the neck may follow next, or the disease may spread down to the biceps and triceps, or with one of its "jumps" it may strike the extensors in the forearm. The flexors in the forearm and the small muscles of the hand may then escape for a considerable time. In very many of these cases in which the wasting begins in the upper limbs, there is a direct spread to the muscles of the back and of the chest. The muscles at the back of the neck are often affected and the patient becomes unable to hold up his head.

In six cases out of sixty the wasting appears to have begun in the peronei or anterior tibial muscles (see Case 6): the intrinsic muscles of

the foot were probably affected about the same time. The calf atrophies next and then the disease spreads upwards over the thigh and hips. Sometimes wasting appears soon afterwards in the small muscles of the hand or in the deltoid. Both legs are usually affected, but I have seen one case in which the right leg was intact although the left calf, thigh and hip were all involved. Cases beginning in this way may present a great resemblance to the Charcot-Marie-Tooth type of atrophy, and it is interesting to note that in at least two reported cases of supposed Charcot-Marie-Tooth disease the patients had Argyll Robertson pupils.

Further course.—Wherever the wasting begins it may at any time become arrested. Some cases cease to progress when one arm has wasted, others may remain stationary for years with both arms rendered completely helpless. The further progress shows considerable variation. Thirty-five per cent. of the cases had some sign of spasticity and a number of these patients afterwards become extremely spastic and develop severe sphincter trouble (see Cases 1 and 5); when spasticity occurs wasting of the lower limbs does not often seem to follow.

In 40 per cent. of cases the knee-jerks were weak or abolished; in some of these cases tabetic manifestations may afterwards develop; but in many of them (23 per cent. of all cases) the wasting becomes generalized—atrophy of the atonic type in all limbs; at, or before, this stage death may be brought about by paralysis of the muscles of respiration.

A point to which I would call attention is that death is rarely due to bulbar involvement as it so often is in idiopathic amyotrophic lateral sclerosis. Bulbar palsies are, in fact, strangely uncommon in these cases and are mentioned only in three cases out of the sixty under consideration.

Fibrillation.—Fibrillation would appear to be less constant than in idiopathic (tonic) cases: it is stated to have been absent at the time of examination in nearly one-third of the cases.

Reflexes.—The tendon-jerks of the wasting muscles usually disappear early and commonly all those of the affected limb; if retained for a time, they steadily decrease. The tendon-reflexes of unaffected muscles are usually normal unless there are signs of spasticity, or of tabes. The superficial reflexes are not often affected by muscular wasting.

Sensation.—Except in the initial stage already referred to, subjective changes are uncommon. The only objective change I have observed

has been a loss of vibration sense in the lower limbs; superficial sensibility and muscle and joint sense have always been normal.

Pupils.—In all but one of the cases in my own experience the pupils have been equal and have reacted normally: in one case they were unequal, but retained their normal reactions. In the cases of the series as a whole the state of the pupils is recorded in forty-two: in seventeen cases (40·5 per cent.) they were normal; in three others (7 per cent.) they were unequal but reacted well to light; in ten others (24 per cent.) they reacted badly; and in twelve cases (28·5 per cent.) they showed the Argyll Robertson phenomenon.

Sphincters.—The state of the sphincters is mentioned in twenty-nine cases; in eighteen they are recorded as normal, and probably we should add to this number most of those in which their condition is not alluded to. In the remainder there were urinary difficulties, always in the direction of incontinence: paralysis of the anal sphincter is uncommon.

Summary.—To sum up the clinical features: The atrophy in amyotrophic syphilitic meningo-myelitis is of the atonic type; it begins with great constancy in one of three situations, it is frequently unilateral, the lower limbs often become spastic, bulbar symptoms are uncommon, severe pain may occur at the onset of the wasting, the vibration sense may be impaired, there may be difficulties of sphincter control. Such characters should, of themselves, suggest syphilis and lead to the examination of the blood and cerebrospinal fluid.

Blood and cerebrospinal fluid.—Of twenty-five cases in which the Wassermann reaction was done in the blood, the reaction was positive in nineteen and negative in six. Of these six cases five had a positive reaction in the cerebrospinal fluid and in the sixth case the cerebrospinal fluid was not examined.

In two cases in which the blood gave a positive result the cerebrospinal fluid gave a negative one, but in both of these cases treatment had been administered for several weeks before the reactions were examined. There is no sure case in which the cerebrospinal fluid reaction was negative before any treatment had been given.

Of seventeen cases in which a cell count was performed in the cerebrospinal fluid, it is stated in seven that lymphocytes were "abundant" or "numerous": in the remaining ten cases the numbers were 42, 19, 6, 75, 150, 2, 49, 6, 8, 44, 10, per cubic millimetre, giving an average of forty-one. No other cells than lymphocytes have been found in any of the cases I have seen, nor are other cells mentioned in the reported cases.

Results of Treatment.

I am unable to say in what proportion of cases antisyphilitic remedies arrest the course of the disease. In four of these uncomplicated (i.e., not tabetic) cases which I have been able to follow, treatment has been uniformly successful. In one patient, who, on account of severe pain, came for treatment at an early stage, there has been a considerable return of muscular power and almost complete cessation of fibrillation. He was at one time unable to raise the left arm to the level of the shoulder, but now all its muscles, with the exception of the extensors of the wrist, are practically as strong as those of the healthy side. The wasting has made little if any progress since treatment was undertaken three months ago, and the Wassermann reaction in the cerebrospinal fluid has become negative.

In another patient treated two years ago the wasting has made no progress since antisyphilitic treatment was given; the Wassermann reaction became negative in the cerebrospinal fluid at the end of the first course of novarsenobillon injections. In two other cases which I have known for several years the disease has made no further progress since antisyphilitic treatment was given. Similar results have been obtained by Nonne [42], Head and Fearnsides [24], Lerouge [34], Vix [54], Lannois et Porot [28], Raymond [44], and others back to time of Graves [20]. Head and Fearnsides obtained a negative Wassermann reaction in the cerebrospinal fluid after treatment in two cases out of four, but were unable by prolonged treatment to render it negative in the other two. Leri [34] believes that antisyphilitic treatment is much more likely to arrest the disease in the early than in the more advanced stages.

Summary.

(1) In my experience syphilis is the commonest cause of chronic spinal progressive muscular atrophy of the atonic type.

(2) Two such cases have been examined pathologically; they both showed: (*a*) a leptomeningitis; (*b*) marginal degeneration of the white matter of the cord; (*c*) very severe destruction of the cells of the grey matter of the cervical enlargement; (*d*) arteritis of the meningeal and intraspinal arteries and perivascular infiltration along the vessels. The first case presented in addition: (*e*) a diffuse degeneration of the anterolateral white matter of the cord; (*f*) ependymitis in the fourth ventricle and iter of Sylvius; and (*g*) granulomatous outgrowths on the ependymal and meningeal surfaces of the medulla oblongata. These changes are regarded as the result of a syphilitic inflammation and

the process may be designated by the term "amyotrophic meningo-myelitis."

(3) The pathological findings, and also certain of the clinical and therapeutic characters, indicate that the disease-process begins in the spinal leptomeninges, and that the destructive influence affects the cord mainly from the surface inwards; the lymph channels probably aid its penetration to the central parts of the cord.

(4) From an analysis of sixty cases the main clinical features are given as follows: atrophy of the "atonic" type beginning (*a*) in the small muscles of the hands, (*b*) in the shoulder-muscles, or (*c*) in the muscles on the outer side of the leg; it may be unilateral or bilateral; its onset is not infrequently preceded by pain; spasticity of the lower limbs may come on; bulbar symptoms are uncommon; the vibration sense may be impaired; there may be difficulties of sphincter control. Argyll Robertson pupils were only present in 28·5 per cent. of these cases.

(5) The Wassermann reaction is negative in the blood in one-third of the cases; there is no sure case in this series in which it was negative in the cerebrospinal fluid before any antisyphilitic treatment had been given.

(6) In four cases, personally observed, the progress of the disease has been arrested by antisyphilitic treatment; similar results have been recorded by others.

My thanks are gladly rendered to Dr. J. G. Greenfield for providing me with pathological material, for helping me often in its study, and for taking most of the photographs with which the paper is illustrated; to Dr. R. T. Williamson for allowing me to examine and make use of his case, and for the loan of the block of fig. 10; to Dr. Aldren Turner and Dr. S. A. Kinnier Wilson for permission to refer to their cases, and to Dr. R. Leslie Dodds for his great assistance in the analysis of cases from the literature.

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THE HISTOLOGY OF JUVENILE AMAUROTIC IDIOCY.

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INTRODUCTION.

AMONG the familial diseases of the central nervous system there appeared for long to be, from both the clinical and pathological aspects, no more clear-cut or invariable type than that first recognized by its ocular changes by Waren Tay in 1881, and more fully described by Sachs six years later. The same symptoms and a similar clinical course characterized all the published cases, and histological changes identical with those first described by Kingdon and Russell [14] in 1897, and more fully studied by Schaffer [17], were found in all the cases subsequently examined. Further, there seemed to be no intermediate cases or links connecting this disease with any other recognized form of cerebral degeneration.

In 1903, however, F. E. Batten [1] described under the title of "Cerebral Degeneration with Symmetrical Changes in the Macula," the clinical features of an affection also characterized by progressive loss of the intellectual faculties, loss of vision and loss of motor power. These cases differed from the Tay-Sachs disease by the fact that they were not limited to the Jewish race, that the blindness was not associated with the same typical ophthalmoscopic picture, that its first clinical manifestations appeared at a later age, and that the progress was slower. The morbid anatomy of this type was later studied by Vogt [25], Spielmeyer [20], Batten and Mayou [3], Bielschowsky [4] [5], and others; the results of their observations, which established the existence of a juvenile type of amaurotic idiocy, indicated its close connection with the Tay-Sachs form, though some of the earlier authors did not venture to regard both forms as manifestations of the one pathological process. During the last fifteen years, however, links connecting the two chief types have been described, some under the title "Late Infantile Form," and pathological investigations have revealed not only

a similarity in the essential neuronic lesions, but have also shown that certain peculiarities of the one type, as atrophy of the cerebellum, may be occasionally found in the other. Further, the extensive degeneration or possibly agenesis of the white matter of the central nervous system found in some of these cases by Westphal [27], Savini-Castano [16], Globus [8], and Ostertag [15], ally this composite group of cases to other degenerative affections of early life, as the Merzbacher-Pelizaeus disease.

The case of juvenile amaurotic idiocy in which we have had the opportunity of examining the nervous system after death seems worthy of record, as it presents some interesting features and serves to supplement the not very numerous observations already published.

The two cases described here belonged to the same generation of a family, the other members of which were, as far as could be ascertained, healthy. The parents came of pure English stock in which no intermarriage with Jews had occurred. A maternal uncle was mentally defective, due it is stated to instrumental delivery at birth, but though unable to read he has earned his own living and served in the Army during the late war. The other collaterals of both parents and their descendants are all healthy.

There were seven children in this family; the eldest, a boy aged 16 (in 1921); the second, C. C., aged 14 (Case 1 recorded here), the third is a boy aged 12; the fourth A.C., aged 8 (Case 2); the fifth and sixth were girls aged respectively 5 and 3; and the seventh a boy aged $1\frac{1}{2}$. All, except the second and fourth, are said to be normal, but it has not been possible to examine them all.

Case 1.—C. C., was first seen in March, 1919. He was then aged 10 years. He had been apparently a healthy and active boy until aged about 9 years, when it was discovered at school that his vision was defective. He was then brought to Mr. Montagu Hine, through whose kindness we have been able to investigate the case.

At first no apparent cause for the failing vision could be discovered, but when he was seen some months later unmistakeable changes were discovered in the retinæ, consisting of very fine granular pigmentary changes in the regions of both maculæ. His vision became progressively worse and when aged about 10 years he had his first epileptic seizure. About the same time he became duller and more listless and apathetic, and later showed signs of gradually increasing muscular feebleness.

He was under the care of one of us in hospital from January to March, 1921. During this time he lay almost constantly in bed, taking little interest in his surroundings. He was slow and inattentive, but when questioned gener-

ally replied intelligently to simple questions. His vision was reduced to about $\frac{6}{60}$ in each eye; it was not possible to obtain accurate records of the state of his visual fields. Mr. Leslie Paton, who examined his fundi, reported extensive macular and perimacular atrophy of the retinæ, extending up to the margin of the discs and for a corresponding radius around the maculæ. In these areas the retinæ were greyish and had fine granular pigmentary deposits in them. The optic discs were of good colour and the vessels normal in calibre and appearance.

His ocular movements were unrestricted and his pupils contracted well on convergence, but sluggishly to light. No disturbances were observed in the functions of his other cranial nerves, except that his speech was slow and rather slurred. The muscles of his limbs were not wasted or spastic and the strength of all was fair, though he was clumsy and rather tremulous in the finer movements of his arms. Gait was slovenly. All the tendon jerks were brisk and the plantar reflexes, which were at first indefinite or flexor, later assumed the extensor type.

While in hospital he had several general epileptiform convulsions which presented no features worthy of note.

After discharge from the wards he continued to attend hospital as an outpatient until August, 1922, when he became too feeble to undertake the journey. During this period he had frequent epileptiform convulsions which occurred more frequently by night than by day. From March, 1921, to March, 1922, he had from two to four or five convulsive seizures each night and often some by day too; then for three months they were less frequent and less severe, but in July they recurred with increasing frequency. His mother stated that in addition to these definite epileptiform attacks he had frequently spasmodic movements of his limbs and face without disturbance of consciousness. His limbs became so feeble that he was wholly bedridden from August, 1922, until his death in February, 1924. Dr. S. R. Smith, under whose care he was during the latter part of his life, informs us that he became totally blind, unable to speak and incapable of turning in bed or moving his limbs. During the latter months of his life there was also complete loss of control over both bladder and rectum. After he became bedridden, strong contractures of his lower limbs developed, the thighs being fully flexed on the abdomen and the legs flexed on the thighs. His arms were in maximal adduction with the elbows flexed and the forearms folded across his chest. He had continuous epileptiform seizures during the twenty-four hours preceding his death.

Case 2.—A. C., the second patient, was sent to me by Mr. Montagu Hine, in December, 1921. He was then aged 9 years. He had been apparently in good health until two weeks previously, when it was reported from school that he was unable to read letters on the blackboard unless close to it. Mr. Hine discovered no error in refraction, but the fundi in the macular regions appeared granular. His central vision was then $\frac{6}{18}$ in each eye. Neurological examination revealed no signs of disease in his central nervous system. The boy was well nourished and well developed, and bright and intelligent for his age.

His vision failed gradually from this time. In April, 1922, his mother noticed that he was becoming more dull and quiet, but no other symptoms were observed until October, 1922, when he had a violent epileptiform fit with convulsions one night in bed. About twelve similar fits occurred during the next three months. In October, 1922, there was a more pronounced granular and pigmentary degeneration of each macular region. He was admitted to hospital in February, 1923, where he remained under close observation for two months.

He was then a well nourished, healthy looking boy; there were no signs of disease in any of his visceral organs. He was, however, very dull and inattentive, slow in response to questions, showed no initiative in conversation and took little interest in what happened in the ward around him. He frequently wetted and soiled his bed and fouled his fingers with fæcal matter.

His visual acuity was reduced to $\frac{6}{60}$ in each eye; no definite restriction could be made out in his visual fields, but it was impossible to make reliable records owing to his inattentive state. The right optic disc was of fairly normal colour, but there was a faint stippling at the macula with a darkish-brown pigment, and some pigmentary change in the retina on the temporal margin of the disc. The left optic disc was paler and of a yellow waxy colour, and there were more marked pigmentary changes in the region of the macula.

His ocular movements were normal and his pupils contracted to light and on convergence. No disturbances were detected in the functions of the other cranial nerves. There was no wasting or alteration in the tone of the muscles of his trunk and limbs, muscular power was good and there was no obvious ataxia, though his movements were usually slow and a little awkward. His gait was unaffected. All his reflexes were normal, but the knee- and ankle-jerks were rather brisk. No alteration in sensation was observed, but it was noticed that he was very tolerant to pin-pricks and other painful stimuli, possibly owing to his dull mental state.

He had nine convulsive seizures during the two months he remained in hospital. Most of these occurred during the night while he was asleep, but several were carefully observed. The onset was always sudden and apparently without warning; a shrill cry usually first attracted attention, then the patient passed into general convulsions which lasted about one minute, in which he became very congested. It is not recorded that he passed urine or fæces or bit his tongue in any attack. After each he appeared more dull for a time and complained of headache. He was given bromide with the aim of checking the fits, but it had little influence. It was then decided to try the effect of novarsenobillon by intravenous injections and he received seven injections varying from 0·15 gr. to 0·6 gr. at weekly intervals, the total amount administered being 2·5 gr. Under this treatment his general condition and his mental state undoubtedly improved, but his vision continued to deteriorate.

During the following year he became more childish, dull and apathetic, took little interest in anything and was able to do little for himself. His vision also

became feebler and the changes in the fundus more marked. They now resembled those described in his brother, Case 1, when he first came under observation. The epileptiform seizures still occur, averaging about one or two a month.

In March, 1924, his vision was only $\frac{6}{60}$ in each eye, and extensor plantar reflexes were obtained for the first time. All the tendon-jerks were exaggerated and a short irregular ankle-clonus could be obtained on each side. He was then much feebler, and though able to walk could not be trusted alone for any distance. He has since been admitted to an institution for mentally defective children.

Pathological Examination of Case 1.

The post-mortem examination was made about thirty hours after death. The body was greatly emaciated and there were extensive bed-sores over the sacrum and great trochanters, and pressure sores on the legs. The skull was rather thick, especially in the occipital region where it measured 1·5 cm. over the torcular Herophili. The brain was of normal size, but the convolutions were rather wider than normal and the pia-arachnoid slightly thickened. The cerebellum, on the other hand, was notably small and much firmer than normal. The cord showed no naked-eye abnormality.

The brain and spinal cord with most of the dorsal root ganglia attached to it were suspended in 10 per cent. formol saline.

The eyes were also removed; the right eye was fixed in 10 per cent. formol in water, and the left in Zenker's fixative.

The *pituitary* was in every way normal. Abundant colloid was present in the pars intermedia, and in the pars anterior a few of the acini in the neighbourhood of the pars intermedia also contained colloid. The proportion of oxyphil to basophil cells did not differ from that usually seen.

The *thyroid* was rather larger than normal, and on section its acini were irregularly enlarged, thin-walled and distended with colloid.

The *thymus* was thin, soft and yellowish. On section it was seen to consist chiefly of fatty tissue with but a few small areas of glandular tissue remaining. A few of the corpuscles of Hassall were seen, the larger of which had become fibrotic and contained very few nuclei; the smaller corpuscles were more cellular. The glandular areas were very vascular, but relatively few lymphoid cells were present; the appearances suggested that the gland had already undergone involution.

The *right testicle* was examined; it was small and showed no evidence of spermatogenesis on section, but otherwise was perfectly normal, containing an abundance of interstitial cells.

The *suprarenals* were thin-walled capsules containing dark liquid material. Section of the cortex revealed a fatty infiltration of its deeper layers, so intense that most of the cells were completely filled with fatty droplets.

The lower lobes of the *lungs* were in a condition of confluent bronchopneumonia, and the liver and kidneys showed evidence of recent passive congestion due to this.

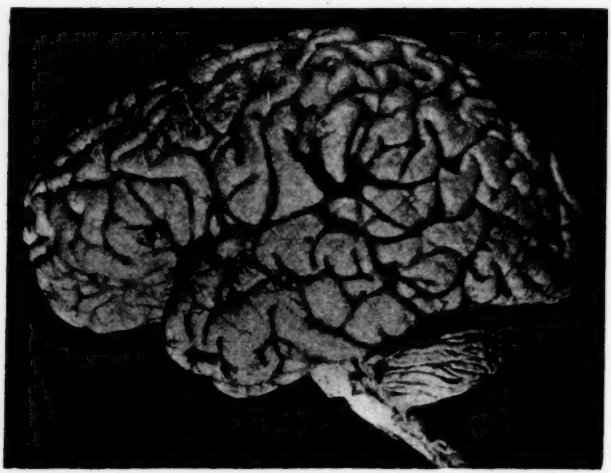


FIG. 1.—Photograph of the brain and cerebellum, showing slight widening of the sulci and great shrinkage of the cerebellum.

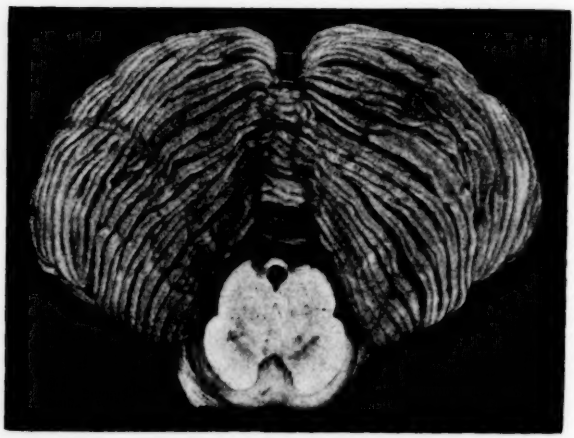


FIG. 2.—Upper surface of the cerebellum, showing atrophy of the folia and the unusual separation of them from one another.

The *heart* and *aorta* were healthy.

The *spleen* was enlarged and softened.

After hardening for ten days the cerebellum, the brain-stem and the left cerebral hemisphere were stripped of pia-arachnoid and photographed. The most striking abnormality was the smallness and firmness of the cerebellum, which was about half its usual bulk. The pia-arachnoid stripped cleanly from it, leaving slender, firm foliæ which stood apart from one another in a very unusual manner. The large sulci between the various lobes were also much more apparent than usual (see figs. 1 and 2).

Each hemisphere was then cut by a horizontal section which passed immediately under the genu and splenium of the corpus callosum. Sections were made parallel to this and 5 mm. apart, the lowest dividing the mid-brain from the thalamus, and the highest passing through the uppermost part of the caudate nucleus. Six slabs of each hemisphere were thus made between these sections. They included the whole of the basal ganglia, the frontal and occipital poles and the island of Reil.

Of these slabs the third and sixth (from the bottom) of the left hemisphere were cut into half, treated with Weigert's fluorchrome mordant, embedded in celloidin, cut and stained for myelin sheaths by the Weigert-Pal method. The two halves of each slab were mounted together so as to give composite sections of the whole hemisphere at the two levels. Other smaller pieces from representative areas of the cortex were stained for myelin in the same way.

From the other slabs pieces were taken which included the whole of the basal ganglia and various regions of the cortex, e.g., the frontal, pre-Rolandic, post-Rolandic, calcarine and hippocampal areas. Those from the right hemisphere as well as pieces from the cerebellum, brain-stem and cord were embedded directly in celloidin, and stained (1) by alum hæmatoxylin and van Gieson's counterstain, (2) by toluidin blue for Nissl granules, and (3) by Mallory's phosphotungstic acid hæmatoxylin for neuroglia fibres.

From similar pieces of the left hemisphere as well as from various sections of the brain-stem, cerebellum and cord (cervical 4th and 8th, dorsal 6th, and lumbar 2nd) frozen sections were made and stained by (1) scharlach R. and hæmatoxylin, (2) Bielschowsky's silver method for neurofibrils, (3) Victoria blue stain for fibrillar neuroglia, (4) the Weigert-Pal method for myelin sheaths.

In addition, Dr. E. W. Hurst undertook the examination by special methods of frozen sections from all these pieces to ascertain as far as possible the nature of the deposit in the nerve cells and in other situations. His results have been included in his paper on the subject [11], and we shall only be able to refer to them briefly.

Nerve Cells.

In the *cerebral cortex* the nerve-cells all showed the type of cell change described by Schaffer in amaurotic family idiocy, but none were affected to so great a degree as is usual in that disease. Most of the nerve-cells appeared as pear-shaped bodies, the apical dendrite and the part of the cell body between it and the nucleus being of normal size and containing well-formed Nissl granules,

while the basal portion of the cell was distended with a granular lipoid substance to about twice its normal diameter. In sections stained by toluidin blue, the granules were highly refractile, almost colourless and appeared to be embedded in a meshwork which took on a faint blue stain. When basal dendrites could be seen they contained well-stained Nissl granules and appeared not to be affected by the swelling of the cell body, but in a few cells all the dendritic processes were irregularly shrunken and stained diffusely with toluidin blue. Others of the nerve-cells were more diffusely infiltrated with lipoid and showed no Nissl granules; while in yet others the lipoid was confined to one side of the cell. Some of the largest pyramidal cells had irregular globular swellings at one of the basal angles of the cell; in these the rest of the cell body was rather more rounded than normal and the Nissl granules in the vicinity of the nucleus were small and granular. The nucleus was very rarely affected, but in some cells it was kidney-shaped and was displaced to one side of the cell-body. Satellite cells were seen round many of the smaller pyramidal cells, but the larger pyramids were for the most part free from them. Everywhere in the cortex there was an excess of small round nuclei, belonging to neuroglial elements.

In sections stained by scharlach R. and hæmatoxylin, the lipoid in the nerve-cells took on an orange-yellow colour, not nearly so bright as that assumed by normal lipochrome pigment. It appeared as large granules apparently lying close together but still easily defined. In this it differed from the lipoid in the cases of amaurotic family idiocy that we have examined, in which the lipoid infiltrated the cell-body more diffusely without forming definite granules.

Bielschowsky's stain demonstrated well preserved neurofibrils which ran from the apical dendrite into a meshwork in the apical part of the cell, and thence, after surrounding the nucleus, passed to the margin of the cell body and along it to the basal dendrites and the axis-cylinder process. It was clear that they took no part in forming the meshwork in which the lipoid granules lay, but were displaced to the periphery of the cell body by the lipoid accumulations. No swellings were seen on the dendrites or axis-cylinder processes by this stain (fig. 3).

Some cells in the hippocampus were rather more diffusely swollen than any others in the cortex, appearing oval in shape with the nucleus displaced to one pole by the accumulation of lipoid in the cell body. With this exception there was no distinction in the degree of cell change encountered between the different regions of the cortex examined. There appeared to be everywhere a definite diminution in the number of nerve-cells, but so far as we could tell this loss affected the layers of the cortex indiscriminately.

In the *optic thalamus* a similar cell change was everywhere present, but some of the large cells in this area showed unusually large granules of lipoid which sometimes attained or even exceeded the size of a red blood corpuscle. Both the large and small cells of the *putamen-caudate* showed considerable alteration. The small cells were more rounded than normal and contained a certain amount of granular material, but this did not stain very brightly with

scharlach R. The large cells were oval and appeared to contain no Nissl substance, the cell body being entirely filled with lipoid granules. The cells of the *globus pallidus* were similarly altered, most of them appearing as pear-shaped bodies, containing a few Nissl granules at their narrower pole, and having the other pole distended with lipoid.

In the *brain-stem* we met with very varying degrees of cell change. For the most part the large polygonal nerve-cells of the motor nuclei showed relatively little alteration. Thus the cells of the oculo-motor nuclei, the facial nucleus, the nucleus ambiguus and the hypoglossal nuclei contained very little more lipoid accumulation than is frequently met with in elderly subjects. But the intra-

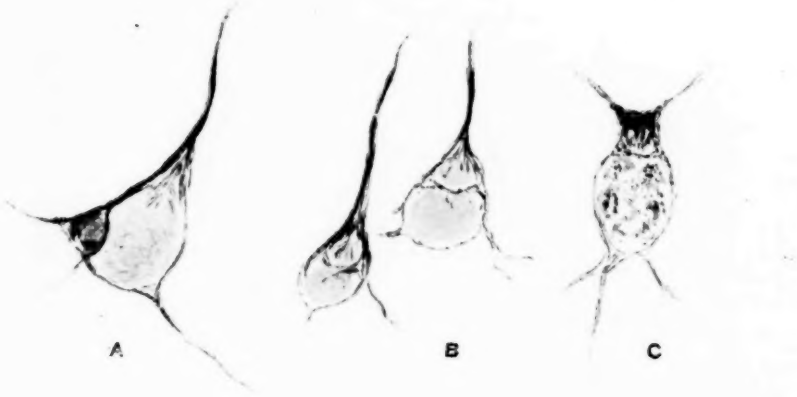


FIG. 3.—Drawings of cells from the cerebral cortex (Bielschowsky's method). A, a large pyramidal (Betz) cell with a lateral accumulation of lipoid; B, smaller pyramidal cells showing the more usual arrangement of the lipoid; C, cell from the hippocampal gyrus.

cellular lipoid, here as elsewhere, differed from normal lipochrome pigment both in staining reaction and in solubility. On the other hand the smaller, more rounded nerve-cells, such as those of the nuclei pontis, the olivary nuclei and the dentate nucleus of the cerebellum, were much more severely affected, and their cell bodies seemed to be completely filled with lipoid granules and to have lost all their Nissl bodies. There was, however, no evidence of disappearance of cells from any of these cell groups, and their nuclei appeared fairly normal. The cells of the mesencephalic root of the trigeminal nerve occupied an intermediate position between these two types of cell, as most of them contained considerable lipoid accumulations, sometimes involving half the cytoplasm of the cell, the rest of the cell body appearing healthy and containing normal Nissl granules.

In the *spinal cord* most of the large motor cells of the ventral horns presented a picture very similar to that of the larger pyramidal cells of the cortex. The apical dendrite and the neighbouring part of the cell body were normal in shape and contained well-formed Nissl bodies, but the base of the cell was distended with lipoid granules. In many of these cells curious bulbous swellings were seen which did not appear to have any relation to the origin of the dendritic processes. But in most the swelling affected the base of the cell more uniformly, so that the cells were pear-shaped (fig. 4).

The degree of alteration varied greatly from cell to cell. Even in one section some of the ventral horn cells might be normal except for a small basal

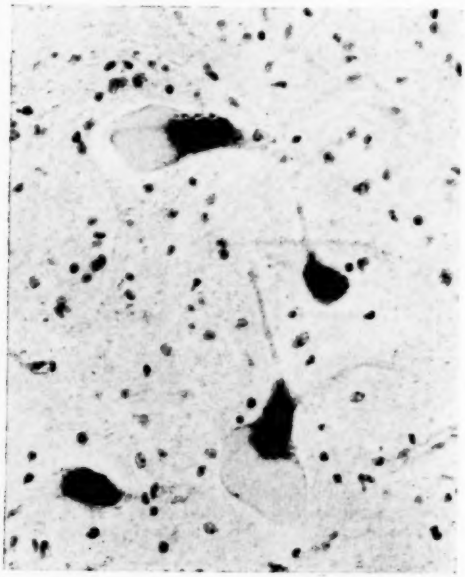
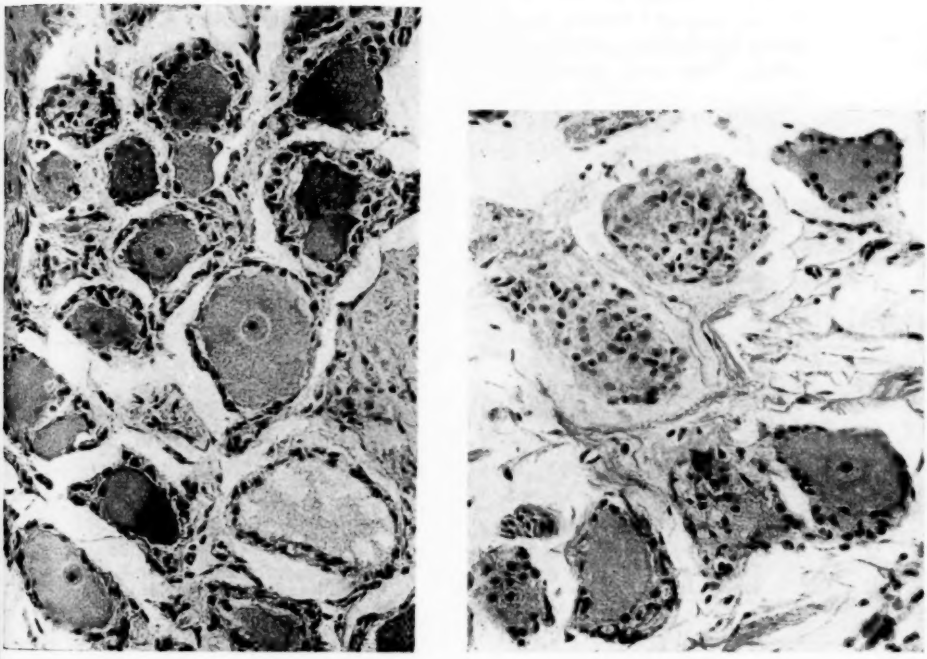


FIG. 4.—Ventral horn cells from the spinal cord stained by Nissl's method (toluidin blue), showing normal Nissl granules at the apices of the cells and accumulations of lipoid at their bases.

accumulation of lipoid, whereas others contained only a few powdery Nissl bodies and a much larger collection of lipoid granules; in some the nucleus was pushed aside by the lipoid so that it lay against the cell membrane. The cells of the lateral horns were, on the whole, less affected than those of the ventral horns and many of them were almost normal. Changes of a similar kind affected the cells of Clarke's column. Here the lipoid accumulation distended the cells evenly and did not lead to any abnormal cell shapes, but in most of them the lipoid was more abundant on one side of the cell body and displaced the nucleus to the opposite side.

In the *dorsal root ganglia* the cells were of very varying size and the amount of lipoid accumulation in them also varied greatly. It was chiefly collected at one pole of the cell, and sometimes caused a bulging at this pole, making the cell oval in shape; but more often the cells retained their spherical outline. Some cells were very little affected; their nuclei were central and well-formed and their Nissl bodies, although small and granular, stained well. In others the nucleus was pushed to one side of the cell, or even against the



A. B

FIGS. 5 A and B.—Sections of dorsal root ganglia showing cells in various stages of vacuolar degeneration and neuronophagy by the capsule cells. (Alum hæmatoxylin and eosin.)

cell membrane. Some cells had shrunken and took up basic dyes more intensely than normal; others again were evidently undergoing vacuolar degeneration, and in some of these the cell protoplasm had been invaded by phagocytic cells which appeared to be absorbing it. Small collections of such cells, which could be seen here and there, seemed to occupy the position of a disintegrated ganglion cell. The capsule cells round the less affected ganglion cells were arranged as a single layer, but round more degenerated cells the

layer was doubled. When the cells were undergoing neuronophagy the capsule cells were seen to multiply at one side of the cell body and to invade the cell protoplasm from that region. The nerve fibres showed no evidence of degeneration, nor was there any increase of fibrous tissue between them (fig. 5).

In the *semilunar ganglia* the cells were affected in varying degree. Most contained a considerable quantity of lipoid granules embedded in a meshwork which stained faintly with toluidin blue. In some all remains of the cells except the lipoid granules had disappeared. Others again were almost unaffected and had plentiful well-formed Nissl bodies, but even in these a zone of lipoid granules could be seen round the nucleus. Such cells presented a picture somewhat similar to that of central chromatolysis. This perinuclear distribution of the lipoid, with retention of the peripheral Nissl bodies, was by far the most common arrangement in the sympathetic ganglia, but was scarcely seen elsewhere in the nervous system (fig. 6).

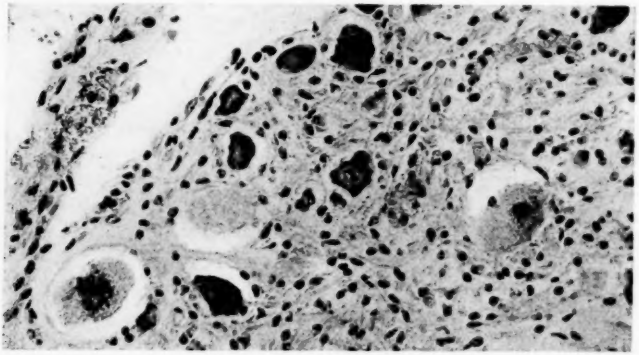


FIG. 6.—Semilunar ganglion; some of the ganglion cells are greatly swollen owing to the accumulation of granular lipoid within them. (Alum hæmatoxylin and eosin.)

In a few cells the lipoid granules did not have this zonal arrangement, but had collected under the cell membrane at one side of the cell and caused a local bulging there. In these the Nissl bodies were perfectly normal in size and distribution, but the nucleus was often pushed to the side of the cell away from the lipoid accumulation. Here and there could be seen a cell which appeared to be disintegrating and undergoing neuronophagy by the capsule cells. Both in the capsule cells and in many of the interstitial cells could be seen numerous fine granules which, with toluidin blue, took on the same violet tint as the Nissl granules; they probably represented the products of cellular degeneration.

Medullated fibres.—With the Weigert-Pal stain the cerebral cortex presented a great diminution in fibres, especially of those of the tangential and supraradial systems. Radially arranged fibres were abundant in the inner one-third of the cortex, and a few could be traced further out; the deeper interradial

system was also fairly well represented, but in the outer two-thirds of the cortex very few fibres could be seen, except a few of the thicker tangential fibres. In the calcarine area Gennari's stripe was present, and under a higher power of the microscope was found to contain a large number of fine fibres.

In the centrum ovale it was noticeable that the optic radiations stood out from the neighbouring white matter by their dark staining. There seemed therefore to be no impoverishment of these fibres, but a definite thinning of fibres of neighbouring systems.

In the brain-stem the only evidence of tract degeneration was a definite pallor of the inner third of the crura in the mid-brain (fronto-pontine fibres). There was no atrophy of the optic tracts, of the fibres of Meynert's decussation, or of the superior cerebellar peduncles; nor was there any evidence of tract degeneration in the cord.

Neuroglia.—In the brain there appeared to be an overgrowth of neuroglia fibres in the subpial layer and small spider cells could be seen in this region; no such neuroglial proliferation could be made out in the subcortical white matter or in the basal ganglia. In the brain-stem and cord the neuroglial fibres stained well and appeared to be rather firmer and more closely set than normal, but we could see no spider cells or evidence of active fibre-formation here.

Finally, it is necessary to mention the accumulation of degeneration products in the Virchow-Robin spaces, which were found here and there in the brain-stem and in the white matter of the cerebrum and cerebellum. Most of these were of a fatty nature, staining intensely red with scharlach R. and dissolving out in celloidin sections. They contained a few doubly refractile crystals or granules, but the larger part of the lipoid was isotropic. In celloidin sections stained by toluidin blue some metachromatic (π) granules were also seen, as well as some collections of fine granules which took up a greenish stain.

No compound granular corpuscles could be seen anywhere in the brain, nor did we find the mulberry-like cells described by Globus in his case.

The meninges showed here and there accumulations of small round cells, but these were very patchy in distribution. No thickening of the meninges, such as has been described in several other cases, could be made out in stained sections. The vessels everywhere were healthy and their walls were not thickened.

The cerebellum.—The changes in the cerebellum were so striking, and of such interest, that we give a special and more detailed description of the lesions in it.

The atrophy, which was so obvious on naked-eye examination, was seen on section to affect chiefly the cortex; in this all the elements were affected to an extreme degree.

The *granular layer* could nowhere be recognized as such; although there were rather more nuclei immediately internal to the zone of Purkinje cells than elsewhere, the difference was very slight indeed. The *molecular layer* was very greatly thinned, but contained rather more nuclei than normally. It

will be seen that the great majority of the nuclei both in the molecular and in the granular layer belonged to neuroglial cells, and not to the small neurons normally present in these situations.

FIG. 7.—Drawing of the cerebellar cortex showing swellings in the outer part of the body and on the dendrites of a Purkinje cell, and absence of basket fibres and of the nuclei of the granular layer. (Bielschowsky's stain.)

FIG. 8.—Drawing of the cerebellar cortex showing two small round swellings on the dendrites of the Purkinje cells near the surface of the molecular layer. (Bielschowsky's stain.)

The *Purkinje cells* were much less numerous than normal, and in some parts of the foliæ were completely absent. Those which remained had not the usual globular shape, but appeared as bizarre root-like structures of very

varying form. The cell body surrounding the nucleus was always smaller than normal, but in almost all the cells it contained a few well-stained Nissl granules at its axonal end. In a few of the cells the Nissl granules were small and powdery. The opposite pole of the cell was enlarged into a bulbous swelling which was continued into the bases of the large dendritic processes originating from it; and at the branchings of these dendrites there were other globular or fusiform swellings, some of which were almost as large as

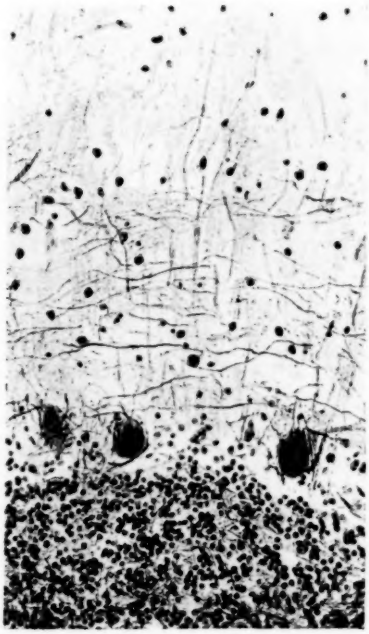


FIG. 9.—Photograph of the normal cerebellar cortex stained by Bielschowsky's method, showing the basket fibres around the Purkinje cells and numerous tangential fibres.

the cell body. Near the surface of the molecular layer where the dendrites broke up into their terminal branches the dendritic swellings appeared as large balls. All these swellings were filled with granular material, which took on a bright orange colour with scharlach R. in frozen sections, and was in every way similar to that seen in the bodies of the nerve-cells elsewhere. As this was the only lipoid substance which could be demonstrated in the cerebellar cortex by this stain, it was easy to count the dendritic swellings, and they were found to outnumber the bodies of the Purkinje cells. The rounded swellings at the termination of the dendrites were less numerous than those

on the branches, but they were considerably larger and being placed nearer to the surface presented a more striking abnormality.

By Bielschowsky's stain the dendritic processes were clearly outlined along their whole extent, and were seen to be rather thicker than normal (figs. 7 and 8). The neurofibrils in them took no part in the dendritic swellings, but were displaced to the periphery by the granular lipoid material. The rounded terminal swellings appeared to be covered with fine hairs which represented the final twigs of the dendrites; these stuck out from the surface

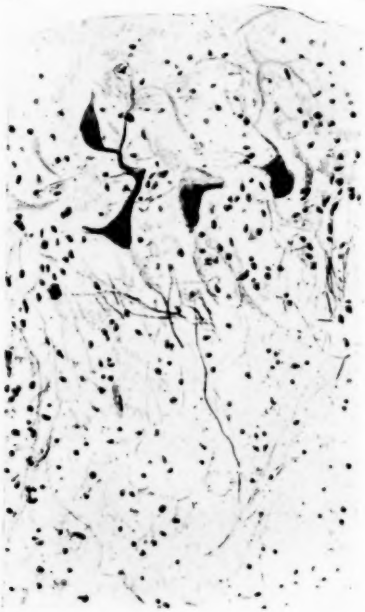


FIG. 10.—Photograph of the cerebellar cortex of Case 1, stained by Bielschowsky's method and photographed under the same magnification as fig. 9, to show the great shrinkage of the molecular layer, and absence of the basket and tangential fibres and of the nuclei of the granular layer.

of the swellings like the spicules on a burr. The axons of the Purkinje cells seemed to run fairly straight into the white substance of the cerebellum and showed no swellings; nor did we see any such reduplication of these axons as has been described by Bielschowsky—although occasionally a process, probably dendritic in nature, arose close to the axon and ran for a considerable distance along the line of the Purkinje cells. Bielschowsky's method also showed that the basket fibres which normally surround the Purkinje cells were entirely absent, and that the radial "climbing" fibres had disappeared almost com-

pletely. The tangential fibres were greatly reduced in number, only a few being present in the zone immediately external to the Purkinje cells; in regions where the Purkinje cells were specially scanty even these had disappeared. These points are rendered obvious by a comparison of sections stained by Bielschowsky's method from the cerebellum of this case and from that of a young healthy adult (figs. 9 and 10).

With the Weigert-Pal stain very little, if any, degeneration of myelinated fibres could be made out; in fact there was an apparent increase in the number

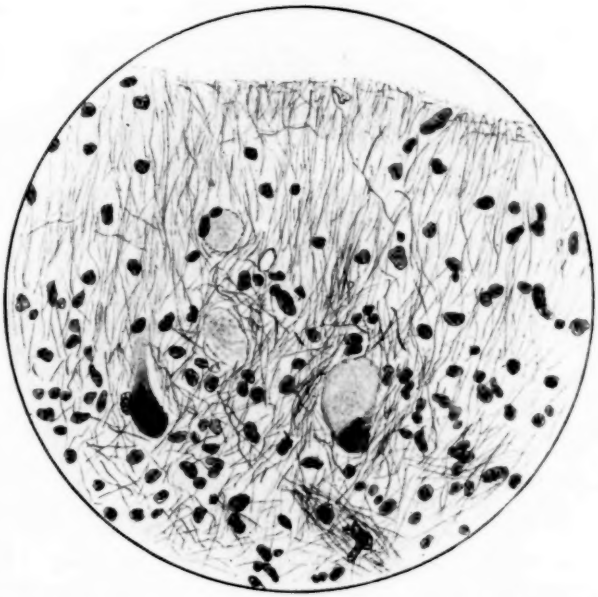


FIG. 11.—Cerebellar cortex stained for neuroglia by Victoria blue, showing a great excess of fibres in the zone from which the granular layer has disappeared, and of radial fibres passing through the molecular layer to the surface.

of fibres in the zone of the Purkinje cells, and more fibres than normal passed just external to these cells. This can be explained by the great shrinkage of tissue which had taken place in the region both of the granular and of the molecular layers of the cortex. There was very little evidence of degeneration in the white matter of the cerebellum, and the proportion of thick to thin fibres did not differ from that in a normal cerebellum.

Sections stained by the Victoria blue method showed an enormous overgrowth of neuroglia fibres, particularly in the region of the granular layer (fig. 11). The majority of the nuclei of this layer appeared, in fact, to be those of spider cells, the processes of which extended for a considerable distance both

inwards to the white matter of the cerebellum and outwards to the molecular layer of the cortex through which they passed to the pia mater in leashes of fine radial fibres. Some tangential neuroglia fibres could also be seen just under the pia mater. There were also a few spider cells in the deeper part of the molecular layer. In the more central parts of the white matter some neuroglial overgrowth was seen, particularly around the vessels, but the felt-work of fibres was nowhere so dense as in the zone from which the granular layer had disappeared.

Collections of lipoid material, which stained a brilliant red with scharlach R., were found here and there in the perivascular spaces in the white matter of the cerebellum, but were not larger or more numerous than those in the centrum ovale of the brain.

Retina.

Owing to the time that had unfortunately elapsed between death and the autopsy certain parts of the retinæ, and especially the rods and cones, had undergone slight post-mortem changes, but as the weather at the time of death was cold these were less severe than might have been expected. One eye was fixed in 10 per cent. formol, the other in Zenker's fluid.

Frozen sections of parts of the retina fixed in formol were treated by scharlach R. Bielschowsky's silver method, and another small part by Cajal's method. A portion of the retina fixed in Zenker's fluid was cut in paraffin, the rest in colloidin and the sections thus obtained were stained by hæmatoxylin with eosin and van Gieson's counterstain, iron hæmatoxylin, and Mallory's phosphotungstic acid hæmatoxylin method for neuroglia.

No part of either retina which was examined was quite normal, but the chief changes were limited to the posterior poles, and were most intense in the regions of the maculæ and between the maculæ and the optic discs; they extended over an arc which measured 17-19 mm. on sections through the centres of the discs and the maculæ. Within this area they were not, however, uniform either in distribution or intensity, and here and there small portions were less severely damaged than the retina round them.

The preparations did not, unfortunately, include the retina in the immediate neighbournood of the ora serrata, but some of the sections extended close to it. In these regions the most prominent change was a diminution in the breadth of the outer nuclear layer. When measured in several sections it was found to be, in relation to the inner nuclear layer in which no lesions were detected, only about one-half of its normal breadth. No other lesions could be seen within it; the size, the shape and the staining reactions of the nuclei were approximately normal, but nearer the posterior pole the nuclear elements were sparser, more irregularly arranged, smaller and shrunken (fig. 12). In the periphery the internuclear layer was also reduced in thickness, sometimes to almost the same degree, and in places it was vacuolated, the vacuoles being separated from one another, mainly by the Müllerian fibres which were unusually distinct. No disease was obvious in the more internal layers, except in the ganglion cells, in which changes similar to those found in the rest of the retina could be seen.

The outer limiting membrane was well preserved in the peripheral zones and rods and cones were visible, but owing to the presence of post-mortem change it was difficult to determine to what extent the latter were affected by the disease; in many places they appeared broken up and partly disintegrated, and here and there they seemed to lie in an unorganized exudate between the retina and the pigment layer. In these regions there were as a rule no visible changes in the pigment cells, which were regularly arranged and heavily laden with pigment. In places, however, granules of pigment could be seen lying between the rods and cones (fig. 12).

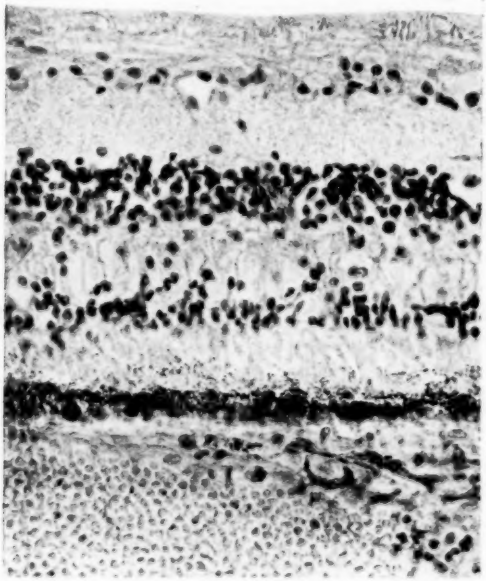


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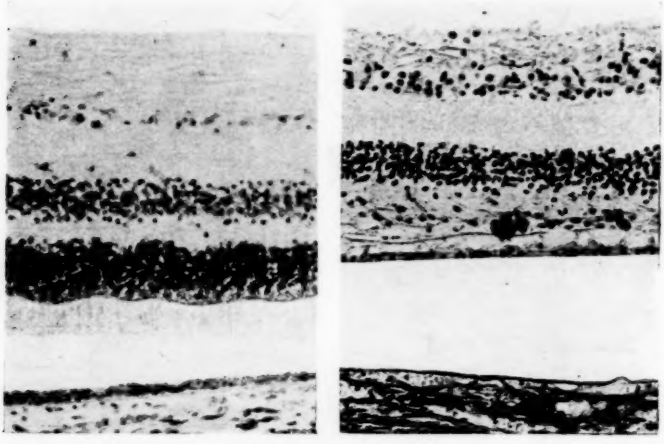
FIG. 12.—Photograph from a section of the peripheral zone of the retina, showing degeneration of the outer nuclear layer, narrowing of the internuclear layer and invasion of the rods and cones by pigment.

Nearer that zone of the retina more severely affected by the disease the internuclear layer shrank and finally became so narrow that the two nuclear layers lay almost in contact. At the same time the elements of the outer nuclear layer became more sparse and finally disappeared. In some places the outer limiting membrane could be no longer seen, and the outer margin of the outer nuclear layer was then irregular and ill-defined; in other regions it persisted as a continuous line in the sections (fig. 13, B). As the elements of the outer nuclear layer became sparse the rods and cones disappeared, or were

unrecognizable in a mass of detritus on the surface of the pigment layer, which was gradually replaced by more organized tissue. The first change in the pigment cells was an irregular loss of the pigment within them, associated with the presence of pigment in the site of the rods and cones, either in the form of scattered granules or large dense spherical masses. The pigment cells at the same time became flattened, less regularly arranged and in some places they could be seen heaped up into two or more layers, suggesting active proliferation (fig. 14). In these regions globular masses of a very finely granular constitution, staining a pale pink with acid fuchsin and resembling hyaline, and sometimes containing a flattened or distorted nucleus on one side, could be seen lying in contact with the pigment cells.



A. B.

FIG. 13.—A, photograph of a normal retina for comparison with B, a section of the affected retina in which the rods and cones and the outer nuclear layer have entirely disappeared and are replaced by sclerotic neuroglia containing migrated pigment. The pigment epithelium is firmly attached to the retina and its cells are irregularly arranged and largely depigmented.

In the more severely affected areas the retina was much reduced in thickness, the only layers that could be recognized being the nerve fibres, the ganglion cells, the inner reticular layer and the inner nuclear layer (fig. 13) A study of a cross-section of such a portion revealed on the outer side of the inner nuclear layer a mass of irregular tissue, considerably narrower than those portions of the retina which it had replaced, consisting of fibrous glia of various degrees of consistence and containing different types of nuclei irregularly distributed within it. In the more sclerosed areas of disease this tissue consisted almost wholly of coarse strands of glia running horizontally, or occasionally obliquely, to the inner nuclear layer. In places it was bounded on its outer

side by a membrane which resembled a thickened outer limiting membrane, and sometimes the latter could be traced into it. Here the retina tended to separate off from the pigment layer, leaving only a single but often irregular layer of epithelial cells more or less devoid of pigment. Frequently, however, the sclerosed tissue was adherent to the pigment epithelial layer, the cells of which were then irregularly arranged and unequal in size (fig. 13, B). Most of the nuclei in this tissue were elongated or spindle-shaped, and contained sparse coarse chromatin granules, but some were much larger and oval in outline.

In other regions, probably where the disease was more recent, the glial tissue was looser and more spongy, and consisted of a meshwork containing, in addition to fibrils, large astrocytes with long processes which seemed to fuse with those of neighbouring cells. In this tissue most of the glial nuclei were smaller and more darkly stained, but some larger and clearer nuclei also existed. Here and there glial cells lay in immediate contact with the pigment cell layer but did not actually invade it. In some of the more severely affected areas it was difficult to distinguish the glial from the pigment cells; it was here that the hyaline globular masses already described on the border of the pigment layer were chiefly found. The proliferated glia extended up to the outer margin of the inner nuclear layer, but actually invaded this only in the very few places where it was thinned and partially degenerated.

In areas of less severe or more recent disease the proliferating tissue contained, in addition to nuclei which were obviously of neuroglial origin, a few elements of the outer nuclear layer and nuclei identical in appearance with those of the pigment cell layer. Neither of these varieties could be, however, identified where the tissue was more firmly sclerosed.

A considerable amount of pigment, identical in staining reactions with that in the epithelial cells, also lay in the sclerosed tissue. In the patches of more recent disease most of it was contained in spherical or ovoid masses so sharply limited as to suggest that they were enclosed within a membrane (fig. 14); sometimes such a membrane could be actually seen, and in a few instances a nucleus similar to those of the pigment cells could be identified among the granules. Some pigment granules were, however, irregularly scattered through the tissue, suggesting the disintegration and rupture of more compact masses. In areas of more advanced disease the pigment was usually accumulated into larger and more irregular clumps (fig. 13, B), but none were as a rule visible in the most densely sclerosed areas. A few granules of pigment were occasionally found around the vessels of the retina, or in their walls, but this was very rare. This migrated pigment frequently extended up to the outer margin of the inner nuclear layer, but could be seen actually within it in very few places, and only where the inner nuclear layer was rarefied or thinner than normal.

The pigment cell-layer was preserved even in the regions of most intense disease, though here it had obviously suffered, and in a few places was not sharply marked off from the sclerosed tissue within it. Its cells were irregularly arranged, often flatter than normal, and there were small gaps in which

none could be recognized (fig. 13, B). Their nuclei usually presented a fairly normal appearance, but in places they were shrunken, irregular in shape and stained very deeply. The most striking change, however, was the great loss of pigment in the cells; some were entirely depigmented and others contained only irregularly arranged granules so sparse that their nuclei could easily be distinguished.

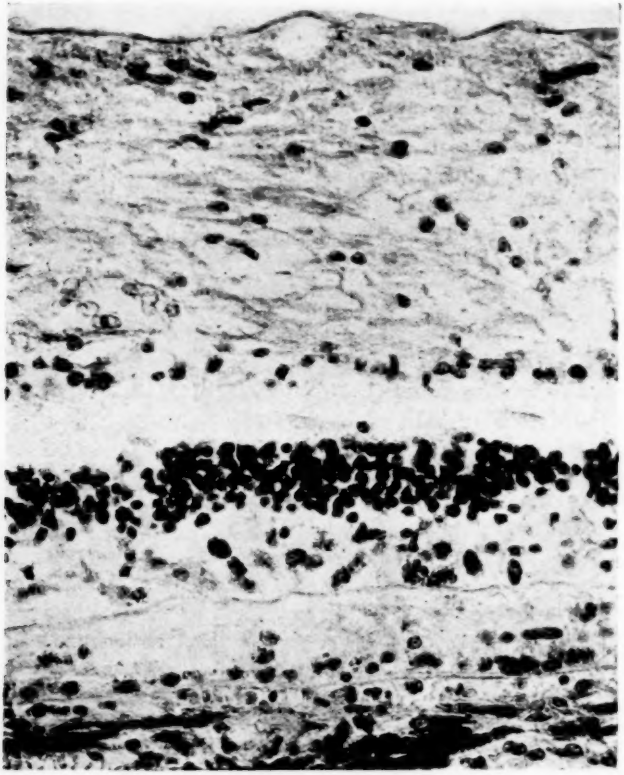


FIG. 14.—Section through a severely degenerated part of the retina showing the absence of its outer layers, the persistence of the outer limiting membrane and proliferation of the pigment cells.

In places there was an obvious proliferation of the pigment cells; here they lay in two or more layers and were more rounded and probably somewhat smaller than the normal epithelial elements. These cells, which were usually devoid of pigment, could occasionally be seen invading the retina or the loose reticular glia that had recently replaced it. There is also direct evidence that

the pigment cells invaded the retina, for nuclei of identical appearance and staining reactions were found in the proliferating glial tissue, and some of the more compact and regularly arranged masses of pigment were contained in cells which we were able, by studying transitional forms, to identify with epithelial elements. It may be, however, that some of these spherical clumps were collected in scavenger cells, but we have been unable to identify such cells in the sections.

Inner nuclear layer.—In the peripheral zones of the retina there was no evidence of disease of the inner nuclear layer, which was well formed and appeared in all respects normal. Even in more affected areas there was usually no obvious change in it, but in the macular region, and between this and the papilla where the lesions were most intense, this layer had in places lost some of its nuclei, and its outer margin was less sharp and well defined than in the normal retina (fig. 14). It was in these places that the proliferating neuroglia extended into the layer, or at least invaded its outer margin, and that a few pigment granules could be seen among its outermost cells.

Ganglion-cell layer.—There was probably no diminution in the number of the ganglion cells in any portion of the retina, but almost all had undergone definite structural changes. Some were obviously swollen and more spherical in outline than the normal cells, and contained granular masses which did not, however, stain with scharlach R.; others were of normal size and shape. Staining by Nissl's method showed that very few retained their ordinary chromatophilic granules, and any of these that remained were irregularly arranged. Unfortunately we did not succeed in impregnating satisfactorily the neurofibrils within the cells by silver, but in Bielschowsky's preparations ovoid or globular swellings were seen on a few of the dendrites, generally at their points of branching. The nuclei of some of the cells, and especially of those which were swollen, were eccentrically placed. There was probably no increase of neuroglia in either the ganglion cell or nerve-fibre layer.

Nerve-fibre layer.—No definite charges could be seen in this layer in sections stained by ordinary methods, and in those impregnated by silver the fibres appeared to be normal in structure and in number. The myelinated fibres of the optic nerves and tracts stained normally by Weigert's method.

Blood-vessels.—Particular attention was given to the blood-vessels of the retina, but no pathological lesions were seen in them.

Choroid.—We have not been able to detect any pathological changes in the choroid or other coats of the eyeballs. The chorio-capillaris was well developed and normal in every respect (figs. 13 and 14).

Discussion.

In this disease the primary changes are obviously confined to the neurons, the proliferation of the neuroglia seen in the most affected parts, as in the cerebral cortex, the cerebellum and the retina, being evidently secondary thereto. In certain parts of the nervous system, as

in the cerebellum and the retina, the disease has an evident selective incidence on certain of the neurons. Thus the granular layer of the cerebellum and the sensory epithelium of the central portions of the retina had completely disappeared, while other systems of neurons in these parts were but slightly affected. Again the fronto-pontine bundles were severely degenerated, while the temporo-pontine and the cortico-spinal tracts remained intact.

The essential lesion of the disease is a special form of degeneration of the cell body, associated with the deposition in it of a peculiar form of lipoid. In many instances the axons undergo a secondary degeneration, but in other systems the axonal processes remain intact, though the cells that give them origin are severely affected.

The finer histological features, as well as the severity of the disease, varied in different systems of neurons, but all belonged to the same type. This was so clearly identical with that described by Bielschowsky and others, that it scarcely requires any further discussion here. Nor do we feel inclined to enter into a discussion on the hypothetical basis of the cell disease, apart from stating our opinion that it is a special form of degeneration dependent on an innate defect in the vitality of the the neurons which appears in the siblings of one family in one generation. The resemblance of the histological lesions and of the clinical features of this disease to those of the infantile type of amaurotic idiocy needs no emphasis, though there are obvious points of difference.

There are, however, certain features of the disease which deserve fuller reference.

Intracellular lipoid.—The reactions to various special methods shown by the intracellular lipoid in our case have been more thoroughly studied by Hurst [11], whose conclusions are embodied in a separate paper. In unstained sections, the lipoid appeared as highly refractile granules with a very faint yellow tinge. By Gram's method we failed to obtain any differential staining of the lipoid; with iron hæmatoxylin it took a faint diffuse greyish stain, while with toluidin blue in Nissl staining it retained a greenish tint, rather more blue than the normal lipochrome. With the Weigert-Pal method it was impossible to stain it at all, even by considerable over-mordanting of frozen sections. With osmic acid also it remained unstained.

In solubility it showed great similarity to lipochrome, as it was insoluble by any fat solvent in twenty-four hours in the cold. It disappeared, however, under treatment with hot xylol and after prolonged immersion in absolute alcohol and ether, as in celloidin embedding.

After treatment of frozen sections by chloroform, or by alcohol and ether for twenty-four hours, it did not take up scharlach R. as intensely as before. This was no doubt due in part to the disappearence of the myelin from sections treated in this way. For as scharlach R. does not act like a stain, but rather becomes dissolved in any fatty material that is present, the rapid wash in 70 per cent. alcohol which follows immersion in the stain may be sufficient to dissolve out the dye from the nerve-cells when no other part of the section is holding it. It was probably for a similar reason that sections of the retina showed no staining of the intracellular granules with scharlach R.

Similarly, in parts of the basal ganglia where there are few myelin fibres, such as the head of the caudate nucleus, the intracellular lipoid was much less intensely stained than in the globus pallidus of the same section.

Hurst considers that in solubility and in staining reactions the intracellular lipoid of this case stands midway between normal lipochrome pigment and the intracellular lipoid substance in the cases of the Tay-Sachs type of idiocy which he examined, but that it differed from both forms of lipoid in not being stained by Kultschitsky's hæmatoxylin after progressive mordanting in Weigert's rapid mordant. He regards it as being composed of phosphatides and cerebrosides.

Cerebellum.

The atrophy of the cerebellum, which was obvious to the naked eye and formed such a remarkable histological feature in our case, is of interest as it serves as a further connecting link between the infantile and the juvenile groups of amaurotic idiocy.

The actual changes in the nerve cells, and especially those visible in the Purkinje elements, were similar in nature to those affecting the cells of the rest of the nervous system, differing from them only in severity. The striking features were the absence of the elements of the granular layer, the diminution in numbers of the Purkinje cells and the loss of the basket fibres surrounding those cells of Purkinje which persisted, combined with a considerable increase of neuroglia in the position of the granular layer. The white matter of the cerebellum was, however, little affected.

Bielschowsky [5] described the same changes in the three cases which he has examined, and they have been also found by Sträussler [23], Brodmann [6], Jansky [13], Batten and Mayou [3] and Globus [8]. In all of these the most striking feature was the loss or

diminution of the granules; Bielschowsky in fact assumed that the disease has a special predilection for, and affects first, these elements. Wandless [26] and Torrance [24] also observed atrophy of the cerebellum disproportionate to that of the forebrain, but the descriptions of the histological changes in their cases are not sufficiently detailed to enable us to recognize the form of the atrophy. A degeneration of the afferent fibres to the cerebellar cortex and disappearance of the basket fibres around the Purkinje cells has been described by Bielschowsky, by Batten and Mayou and by Brodmann.

In many of the cases undoubtedly belonging to this disease, as in those recorded by Vogt [25], Speilmeyer [20] and Dide, Guiraud and Michel [7], the cerebellum was not atrophied, nor did it show more evidence of neuronal degeneration than the rest of the central nervous system. The same remarkable swellings of the dendrites of Purkinje's cells with a deposition of granular lipoid material within them, were found by most of the authors, and also in several cases in which there was no gross atrophy of the cerebellum, as in the cases recorded by Schob [19] and Rogalski.

The recorded cases of juvenile amaurotic idiocy may be consequently divided into two groups, one in which the cerebellum had undergone general atrophy and was more severely affected than the rest of the brain, the elements of the granular layer and the afferent cortical fibres being particularly involved; and a second in which the cerebellum was only affected to the same degree as the rest of the nervous system. The explanation of the more severe degeneration in the cerebellum is not easy. There can be now no doubt that it represents an essential part of the disease and is not merely a chance association, as Sträussler and even Bielschowsky originally thought. It is interesting in this connection that Higier in 1906 [9] suggested on clinical grounds a relation between cerebellar atrophy and amaurotic idiocy, and that Dide, Guiraud and Michel's case was originally published as hereditary cerebellar ataxy with retinitis pigmentosa. A review of the literature, however, shows that in many of these cases, as in our own, symptoms of cerebellar deficiency were absent or at least inconspicuous, possibly because they were obscured by the paresis and other clinical manifestations of the disease. This fact invalidates Bielschowsky's assumption that the cerebellum is in these cases the first part of the nervous system to be affected, and that the disease in it may date from early childhood or fœtal life; our patients were normal in all respects and particularly skilful at games until diminution of vision and epileptiform convulsions

set in, so it seems impossible that there should have been in them any serious structural change in the cerebellum before the retina and the forebrain were involved. Consequently it is difficult to believe that the globular swellings on the axons of the Purkinje cells, the numerous lateral branches on these and the bending back of the axons towards the molecular layer, which Bielschowsky, Brodmann and Batten and Mayou observed, can have been due to damage of these fibres in early life by the sclerosis of the granular layer. Further, Bielschowsky's hypothesis that the absence of the Purkinje baskets is due to destruction of the afferent cortical fibres by such a sclerosis is made improbable by the fact that in our case the glial overgrowth in the granular and supra-granular layers was only moderate in degree, and appeared to be secondary to the disappearance of neurons.

It seems more probable that the explanations of the cellular and fibre degenerations in the cerebellum is that certain nerve elements in this organ, and especially the granules, are more vulnerable to the disease, which is certainly not of uniform severity through the whole nervous system. In this connection, the fact must be borne in mind that in many of the recorded cases there has been a selective incidence on certain systems of fibres, as on the fronto-pontine bundle in one of Bielschowsky's cases, and in our own.

The especially intense affection of the cerebellum in many cases of juvenile amaurotic idiocy seemed, at first, to be a point of distinction of this form from the infantile type of the disease, but there are now several cases of the true Tay-Sachs type, race-limited to the Jews, in which the cerebellum was severely involved. In 1911, Holmes [10] described advanced atrophy of the cerebellum, as seen by the naked eye, in a boy who died at the age of 2 years and 10 months. His sister was a typical case of the Tay-Sachs disease, and the characteristic changes were found in her nervous system by Carlill and Mott. The molecular layer of the cortex in Holmes's case was of normal breadth, but the granular layer was very narrow and its cells very sparse. The Purkinje cells were also reduced in number and had undergone the typical changes found elsewhere in the nervous system. There was considerable glial sclerosis, especially in the zone of the Purkinje cells. As the material had been fixed in alcohol, a complete examination of the cellular changes was impossible. In this case the forebrain was abnormally large, weighing 1,450 grm., and there was an extraordinary amount of neuroglial proliferation in both the grey and the white matter. Bielschowsky [5] later recorded a very similar case in a

Jewish child who died at the age of 2 years and 7 months; the folia were widely separated, the molecular layer narrow, Purkinje cells few in number and the granules very sparse. The white matter of the cerebellum was partly degenerated and the fibrillar baskets of the Purkinje cells had disappeared. It is interesting that in this case, too, the brain was abnormally hard and large, weighing 1,690 grm. Savini [16] also described a megalocephalic brain in a Jewish child who died at the age of 2 years and 2 months; it weighed 1,530 grm. In this case, too, the number of the Purkinje cells was reduced, but the granular layer was apparently unaffected. There was, however, a lack of myelination in the whole brain which he attributed partly to agenesis, partly to degeneration. A great increase of neuroglia was present.

Westphal [27] also found a loss of Purkinje cells and a great increase of neuroglia in the cerebellum; and Ostertag [15] observed a similar change, and, in addition, a diminution of the granule cells and loss of the afferent cortical fibres, in an atrophied cerebellum from a case of the Tay-Sachs disease. Globus [8], who has recently contrasted the cerebellar lesions in the Tay-Sachs and juvenile groups, found in two cases of the former a general atrophy of the cerebellum, a great diminution of the Purkinje cells, a thinning of the granular layer, diminution of the white matter, and in one case absence of the moss and climbing fibres.

This review shows that, in addition to the typical changes in the cells, cerebellar lesions resembling those described by Bielschowsky and others in the juvenile form of amaurotic idiocy, also occur in the infantile or Tay-Sachs disease, but they vary from case to case both in type and in severity. This fact is a further argument for the thesis that the Tay-Sachs and Vogt-Spielmeyer types are only manifestations of the same pathological process, the histological differences being mainly dependent on the mode of reaction of the nervous tissues, and the incidence of the disease on special structures.

It is in this connection interesting that in a few cases lesions have been described which tend to ally amaurotic idiocy to other degenerative nervous diseases of early life, as the extensive degeneration of the white matter of the brain observed by Savini [16], Globus [8] and others, which resembles in many respects that found in Merzbacher-Pelizaeus, disease.

Retinal Lesions.

The most striking feature in the histological changes in the retina was undoubtedly the degeneration of its outer layers and their replacement by proliferated neuroglia, while the inner layers, that is the nerve fibre, ganglion cell, inner reticular and inner nuclear layers, remained intact or were affected much less severely.

It was luckily possible to trace the evolution of these lesions by studying the retina from its peripheral zones where there was little change, towards the macular region where the disease was most intense. Such a study shows that the earliest recognizable lesion was a breaking-up of the rods and cones, associated with a rarefaction and narrowing of the outer nuclear layer. It seemed impossible, in our sections at least, to determine whether the disease commenced in the rods and cones or in their cell-bodies in the outer nuclear layer, but the fact that even in the earliest phases of the disease degenerative changes were recognizable in the internuclear layer, in which the efferent processes of the rod and cone elements arborize, suggest strongly that the disease first affected the cell-bodies of these elements and thereby led to a degeneration of both their afferent and efferent processes, or that it involved simultaneously the whole neuron unit. The former view corresponds more closely with the neuronic changes found in the rest of the central nervous system.

The next stage was the replacement of the degenerated external layers of the retina by proliferating neuroglia, followed by a proliferation of the pigment epithelial cells and an invasion of the degenerating retinal layers by them. The changes in the pigment cell layer were probably all secondary to the lesions in the other layers of the retina.

It is true that in a few places there was an obvious loss of elements in the inner nuclear layer. As the only nuclei affected were those of the outer border of the layer which were in immediate contact with the degenerated tissues, and as these changes in the inner nuclear layer were found only where the glial proliferation was intense, they may be regarded as secondary. It could scarcely be expected that all these elements should persist unchanged after their processes in the sclerosed internuclear layer had been destroyed.

In addition to these pronounced degenerative changes in the outer layers of the retina, there was an affection of the nerve cells of the ganglion layer similar to that which was found in the cells of the central nervous system.

The number of cases in which a careful histological examination of the retina has been made is still limited, but in all of them more or less similar changes have been found.

In 1908, Stock [22] published his findings in the retinæ of three of Spielmeyer's original cases, and as in one of these he was able to fix the eyes within a short time of death his descriptions are particularly valuable. The choroid was normal, apart from a slight endarteritis of some of the vessels, and the chorio-capillaris was intact. The chief changes were found in the outer layers; in the two most advanced cases the rods and cones and the outer nuclear layer had entirely disappeared, in the third and least advanced all layers were present in the periphery but approaching the posterior poles of the eyes the rods and cones disappeared, their nuclei became smaller and paler, and near the maculæ they were no longer visible. As the nervous elements degenerated the pigment cells became irregular in size and arrangement, and in places some had undergone proliferation and had grown into the degenerating layers of the retina. Within these there were also numerous masses of pigment granules, chiefly in the sheaths of the vessels, to which they were carried either by the wandering epithelial or by glia cells. The outer limiting membrane could be seen in places, but was apparently not continuous; between it and the pigment layer there was a palely-stained vesicular structure which probably represented the remains of the rods and cones. The inner nuclear layer was well preserved, though a little thin in places. There was apparently no loss of ganglion cells, except around arteries in which there were endarteritic lesions, but their protoplasm had undergone changes similar to those found in the cells of the central nervous system. The nerve-fibre layer and the optic nerves were intact. There was a dense glial sclerosis in the site of the degenerated outer nuclear layer. Stock concluded that the changes were due to a primary degeneration of the neuro-epithelium and a secondary proliferation, combined with regressive changes, of the pigment epithelium.

Ichikawa [12] in the same year described the retinal changes in a Japanese patient who had died at the age of seven years after two years' illness. Here also the choroid and chorio-capillaris were normal, while the rods and cones as well as the outer nuclear layer had disappeared completely, except in small areas near the periphery of the retina; they were replaced by dense glial tissue which contained masses of pigment granules. The inner nuclear layer, however, presented evidences of a progressive degeneration. The ganglion

cells stained diffusely and contained vacuoles, and the nerve-fibre layer was thinner than normal, but the optic nerves presented no changes. Ichikawa interpreted these changes as a uniform degeneration of all the nervous elements of the retina, allied to that which occurs in retinitis pigmentosa.

Brooks, in a case published by Wandless [26], found all layers of the retina so severely degenerated that the normal strata could not be recognized. He was unable to find any ganglion cells in the retina or nerve fibres in the optic nerves, but Marchi's method revealed in the latter droplets of fat which he regarded as indicating degenerated fibres. The record of this case is incomplete.

Bielschowsky [5] records that in his cases there was complete absence of the rods and cones and of the outer nuclear layer, and an overgrowth of neuroglia in their place, but there was no noteworthy wandering of pigment. The ganglion cells had undergone the same changes as other cells of the nervous system, and were also reduced in number; as a result of this there was a slight degree of optic atrophy.

Mayou [3] was able to examine the eyes of one of Batten's cases under satisfactory conditions, as both bulbs were injected with Zenker's fluid immediately after death. The choroid was normal, but there was an irregularly distributed degeneration of the retina, most intense in the macular region. Here there was a complete disappearance of the ganglion cells, of the inner nuclear layer and of the rods and cones, and in addition some thickening, probably owing to glial proliferation, of the inner layers. Pigment which had migrated from the pigment cells had invaded the outermost layers. He believed that the disease commenced in the ganglion layer, where the cells swelled, lost their Nissl substances, sometimes became vacuolated and eventually disappeared. This was followed by an œdema of the internuclear layer, gradual disappearance of the inner nuclear layer and of the rods and cones and finally by migration of pigment.[1]

Dide, Guiraud and Michel [7] have recorded the histological changes in a case which was originally published by Frenkel and Dide as

[1] Mr. Mayou has pointed out to us that owing to a printer's error the outer nuclear layer was described as the inner nuclear layer in his paper. He has kindly allowed us to examine his sections, which show changes very similar to those in our own case. There is, however, a more widespread degeneration of the outer layers of the retina and less neuroglial sclerosis, possibly owing to the more acute course of the disease, which began at 3½ years of age and led to death at the age of 6 years. There is also less evidence of proliferation of the pigment epithelium, although the degenerated areas contained large clumps of pigment. The inner nuclear layer is on the whole well preserved, though in a few places it is slightly rarefied.

"Héredo-ataxie cérébelleuse avec rétinite pigmentaire," but the alterations in the central nervous system leave little doubt that it belonged to the juvenile type of amaurotic idiocy. The retinal lesions were, as in most cases, diffuse and patchy. The most characteristic changes were found in the ganglion layer, which was irregular and had lost many of its cells; the persisting cells were enlarged and their cytoplasm stained badly and contained vacuoles and a lipoid deposit. The internuclear layer was absent in places, and the two nuclear layers had undergone degenerative changes. Even the normal portions of the retina were infiltrated by pigment, which extended as far as the ganglion cells. Around the capillaries were fusiform cells with clear, oval nuclei, which were regarded as mesodermal cells of choroidal origin.

Torrance [24], in three cases of the late infantile group, in all of which there was optic atrophy, and in two patches of pigment in the periphery of the fundi, observed diminution of the ganglion cells, narrowing of the outer nuclear layer and degeneration of the rods and cones.

From this review of the retinal changes that have been described, we find that, as in our own cases, no disease, apart from slight thickening of the vessels, has been detected in the choroid or chorio-capillaris, but, unfortunately, no mention is made of these structures in some of the publications. The changes in the retina itself have varied both in intensity and distribution; from many of the descriptions it is obvious that they were patchy and irregular, but they were always most intense in the region of the maculæ.

Apart from changes in the ganglion cells, which were similar to those found in all nerve cells, the cases may be divided into three groups by the histological lesions in the retina. In the first group, which contains the cases of Stock, Bielschowsky, and our own, only the outer layers of the retina had suffered, any changes visible in the inner layers being probably secondary thereto. In the second group, including the cases of Mayou, Dide and Torrance, the attention of the authors was arrested mainly by changes in the inner layers, especially in the ganglion cells, but Mayou and Torrance also found the rods and cones absent; these are not referred to by Dide, Guiraud and Michel. Finally, Brooks found all layers of the retina so severely degenerated that he could not recognize them, and Ichikawa regarded the condition as a uniform (*gleichmässig*) degeneration of all nervous elements, though in his case the outer layer had obviously suffered the most severely.

There are, consequently, variations in the retinal lesions from case to case, analogous to the varying severity and distribution of the disease in different parts of the central nervous system. These variations cannot be explained by the duration of the illness; Batten and Mayou's case died at the age of $5\frac{1}{2}$ years, Torrance's three cases under $4\frac{1}{2}$, while Ichikawa's case was 7 years old at the time of death. On the other hand, in some cases where the retinal lesions were less extensive the disease had lasted longer and terminated at a later age.

The retinal ganglion cells seem to suffer invariably, and though many of the histological descriptions leave much to be desired, it may be accepted that they undergo the same changes as the cells in the rest of the nervous system. In addition, however, there have been, in all the cases hitherto examined, lesions in other layers of the retina, either limited to the neuro-epithelium, or extending to the inner layers as well. These lesions of the inner layers may be primary, or they may be secondary to the affection of the neuro-epithelium, since the rule is that retinal degenerations extend from without inwards.

The retinal changes in the juvenile type of amaurotic idiocy may be therefore defined as a primary change in the ganglion cells, combined with an independent degeneration of the outer neuronic elements of the retina, which in some cases extends to the inner nuclear and inner reticular layers. This degeneration is followed by a glial sclerosis of the affected areas, and a proliferation of the pigment epithelium cells which wander into the degenerated tissue.

It is this affection of the outer layers that distinguishes the retinal lesions of the juvenile from those of the infantile type of family amaurotic idiocy. In the latter, the essential changes are confined to the ganglion cell layer, though œdema of the internuclear layer has been described. Savini-Castano and Savini [16] have, it is true, described loss of the outer segments of the rods and cones in a rather exceptional case, but this was probably a post-mortem change.

Vision and Ophthalmoscopic Changes.

The blindness, which is so frequently an early symptom, must obviously be attributed to the degeneration of the sensory neuro-epithelium: there is often a considerable degree of amblyopia when there is no visible pallor of the disc or other change in the fundus oculi. Since the pupillary reactions fail gradually as the blindness progresses, the amaurosis cannot be due wholly to changes in the visual cortex, though in some cases these are severe.

There have been considerable variations in the ophthalmoscopic appearances in the cases of the juvenile form of amaurotic idiocy hitherto described. In many they resembled those present in our own patients, and this is probably the most typical picture. They commence with a small white area at the macula, surrounded by a reddish ring. As these macular changes become more pronounced, the atrophy extends further into the retinæ which then has a streaky white appearance, speckled over with black pigment; eventually the whole retina appears atrophic and pigmented. But in some cases, as in Bielschowsky's patient, there was no visible pigmentary disturbance although the retinæ were atrophied; in others pigment was visible only in the periphery of the fundus, as in two of Torrance's cases, or was more prominent in the periphery, as in Batten and Mayou's case. There may be, however, neither blindness nor retinal changes, as in a case recorded by Schob [19] in which the other clinical symptoms and the pathological changes were characteristic. Neither the age of the patient at death nor the duration of the condition can explain the variability in the degree of pigmentation of the retinæ, as there is no parallel between it and either the age at the onset of the disease or its duration.

In almost all cases, however, the optic discs were abnormally pale, though the visible atrophy was frequently noted only some time after loss of vision had become a pronounced feature. However, in some cases, the optic atrophy was of slight degree even in the advanced stages of the illness, or was absent, as in Spielmeyer's patients. This conforms to the observation that in some cases, as in Batten and Mayou's, in Stock's and in our own, no loss of fibres could be determined in the optic nerves by histological methods, and to the fact that the actual loss of ganglion cells and nerve fibres in the retinæ was usually slight.

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THE PATHOGENESIS OF SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD WITH SPECIAL REFERENCE TO ITS CONNECTION WITH ADDISON'S (PERNICIOUS) ANÆMIA, ACHLORHYDRIA AND INTESTINAL INFECTION.

BY ARTHUR F. HURST, M.D.OXON.

THREE years ago J. R. Bell and I published [3] the results of our investigations on eight cases of subacute combined degeneration of the spinal cord. We concluded, as Byrom Bramwell had done before, that the anæmia with which this disease was known to be associated since its first description by Risien Russell, Batten and Collier, was of the Addisonian (so-called "pernicious") type, and was not, as had generally been believed, a non-specific secondary variety. This view was supported by our discovery that the achlorhydria, which is constantly present in Addison's anæmia, was also present in all of the eight cases of subacute combined degeneration which we had examined, and we discussed the bearing of this fact upon the pathogenesis of the two associated diseases. I have now had the opportunity of investigating the condition of the alimentary canal in twenty-four cases of subacute combined degeneration of the cord and of thirty-six of Addison's anæmia, many of which had also symptoms or signs of organic nervous disease. In the present paper I shall discuss the results of our investigations and show how they bear upon the view expressed in our first publication, that these conditions are due to the association of oral sepsis with the absence of free hydrochloric acid throughout digestion, and the consequent intestinal infection and toxæmia.

As I believe that the signs and symptoms of nervous disease, which are observed sooner or later in about 80 per cent. of cases of Addison's anæmia, are due to subacute combined degeneration of the cord, and that the anæmia, which develops in almost all cases of the spinal disease before death occurs is of the Addisonian type, the division between the two associated diseases is quite artificial. For the purpose of this paper I have classified those cases in which the patients first sought advice on account of symptoms due to anæmia

as examples of Addison's anæmia, however marked the nervous symptoms ultimately became, and those who first complained of nervous symptoms as examples of subacute combined degeneration of the cord, even if death ultimately occurred as a result of anæmia.

Achlorhydria.

It is now universally agreed that complete achlorhydria is present in all or nearly all cases of Addison's anæmia. It was present in all of my own series of thirty-six cases examined by means of a fractional test-meal. In Table I (b) the results obtained by six other authors are recorded; complete achlorhydria was found in all but 10 of 579 cases, making a percentage of 98·3. Levine tells me that he doubts the accuracy of the observation in the three exceptions to the 108 cases collected by him and Ladd, and Strieck is similarly doubtful about the two exceptions in his 165 cases.

Table I.—Frequency of Achlorhydria.

(a) *New Lodge Clinic and Medico-Neurological Unit, Guy's Hospital, 1920-1924.* (*Fractional Test-meals.*)

	Number of cases	Achlorhydria	
		Number	Percentage
Normal (Bennett and Ryle, Guy's Physiological Department)	100	4	4
Various medical diseases	762	86	15
Carcinoma of stomach	25	15	60
Chronic appendicitis (Bonar, Guy's Surgical Wards)	65	22	33
Gall-stones (Bonar, Guy's Surgical Wards)	35	17	49
Rheumatoid arthritis (A. F. H., Faber, Kahlmeter, Coates and Gordon)	150	59	40
Addison's Anæmia	36	36	100
Subacute Combined Degeneration of the Cord	24	24	100
Tabes dorsalis	13	1	7·7
Disseminated sclerosis	10	0	0

(b) *Other Authors* (*mostly Ewald Test-meals*).

Addison's anæmia	Ewald	75	75	98·3
	Zadek	50	50	
	Weinberg	105	105	
	Levine and Ladd ..	108	105	
	Faber	76	71	
	Strieck	165	163	
Subacute combined degeneration ..	Faber, 1898 ..	1	1	100
	Barker, 1919 ..	2	2	
	Vanderhof, 1923 ..	29	29	
	Sheard, 1924 ..	3	3	
	Gordon, 1924 ..	1	1	
	Szlapka	1	1	
	Garvey and Stern ..	1	1	
	Worster-Drought ..	6	6	

In our original paper Bell and I recorded that complete achlorhydria was present in all of the eight cases of subacute combined degeneration of the cord we had investigated. We have now had fractional test-meals given to twenty-four cases, which include all those which have come under the observation of my colleague, Dr. C. P. Symonds, at Guy's Hospital, and complete achlorhydria has been found in every instance without a single exception.

In our first paper we were only able to refer to two other cases, both recorded by Barker, in which test-meals had been given, and in these achlorhydria was found. Professor K. Faber [1], of Copenhagen, has drawn my attention to a case published by him in 1898 in which achlorhydria was present; the nervous symptoms had preceded the onset of typical Addison's anæmia by several months. Our results have been strikingly confirmed by Vanderhof [8], who, in a paper published shortly after ours, described the results of gastric analysis in a consecutive series of twenty-nine cases of subacute combined degeneration of the cord; complete achlorhydria was found in all. The only other published cases are three of Sheard's [6] and one each of Gordon, Szlapka [7], and Garvey and Stern [2], in all of which achlorhydria was present. Dr. C. Worster-Drought tells me that complete achlorhydria was present in all of the six cases of subacute combined degeneration of the cord whose gastric contents he has examined. Whatever exceptions may be found in the future, the fact that complete achlorhydria was present in all of the sixty-eight cases recorded up to now shows that the absence of free hydrochloric acid from the gastric contents must be a very important if not essential factor in the pathogenesis of subacute combined degeneration of the cord.

The complete achlorhydria is present in the earliest as well as in the last stages of the disease and during remissions, and whether anæmia or the nervous disease is present alone, or whether the two are associated together. It differs from the achlorhydria of cancer of the stomach and phthisis in being a predisposing cause and not a symptom, for in these conditions its development can be watched as the disease gets worse, instead of being always fully developed from the earliest moment of observation. Moreover, the achlorhydria is always complete: when the ordinary Ewald test-meal was replaced by the fractional method, the percentage of cases of growth of the stomach with achlorhydria fell from 80 to 60, but in Addison's anæmia and subacute combined degeneration of the cord the percentage has remained 100.

(*a*) *Constitutional Achylia Gastrica.*

The achlorhydria is generally due to constitutional achylia gastrica, an inborn error of functional activity independent of anatomical changes in the mucous membrane. About four per cent. of normal individuals have this condition (Bennett and Ryle). It is probably often familial, though opportunities of investigating this point do not frequently arise, as many people with achylia have no symptoms, but Albu has observed it seven times, Udaonda and Jung once each, and I have had under my care a brother and sister and two sisters with digestive symptoms caused by achylia gastrica. (Table II (a)).

TABLE II.—FAMILIAL OCCURRENCE OF ACHYLIA GASTRICA, ADDISON'S ANÆMIA AND SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD.

(a) *Achylia Gastrica.*

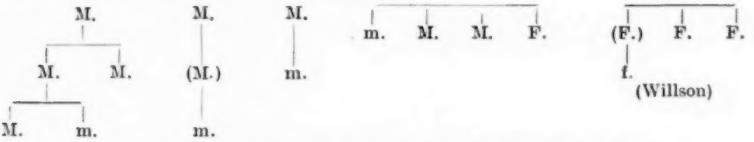
Eleven recorded families (Albu 7; Udaonda 1; Jung 1; A. F. H. 2).

(b) *Addison's Anæmia.*

Forty-nine recorded families, varying between 2 and 6 in a family, in 1, 2 and 3 generations (Gulland and Goodall 5; Bramwell 1; Gilbert and Weil 1; Patek 1; Bartlett 1; Matthes 1 Roth 1; Faber 1; Levine and Ladd 9; Cabot 2; Schauman 6; Meulengracht 1; Mustelin 1; Gilford 2; Charles Hunter 3; Tscherning 1; Klein 1; Decastello 1; Minot 1; Panton, Maitland-Jones and Riddoch 1; Caccini, Morris and Falconer 3; A. F. H. 6).

(c) *Subacute Combined Degeneration of the Cord and Addison's Anæmia.*

Five recorded families (Willson 1; A. F. H. 4).



[Capitals = A.'s A.; small letters = S.C.D.; brackets = neither.]

(d) *Addison's Anæmia and Achylia Gastrica.*

Fifteen recorded families, in two of which more than one had Addison's anæmia (these are not included in No. II). (Martius 3; Queckenstedt 1; Weinberg 7; Schauman 1; Faber 1; A. F. H. 2.)

The familial occurrence of achylia gastrica must be the explanation of the familial occurrence of Addison's anæmia, which has been recorded by many observations (Table II (b)). I have been able to collect no less than forty-four family histories from the literature, and six out of my series of thirty-six cases of Addison's anæmia had one or more relations who had died of the disease.

Willson [9], in 1912 described the case of a woman with subacute combined degeneration of the cord, two of whose maternal aunts had died of Addison's anæmia. I have met with a similar family history in four out of twenty-four cases of the disease (Table II (c)). The

father of one patient, the paternal grandfather of another, and two brothers and a sister of a third died of Addison's anæmia. The most remarkable case was that of a doctor who died of subacute degeneration of the cord, associated with achlorhydria and Addisonian anæmia; his brother, father, paternal uncle and paternal grandfather had all died of Addison's anæmia.

The sister of a woman who consulted me for chronic diarrhœa, which was found to be due to achlorhydria, had died of Addison's anæmia. Another woman with pyelitis, who had had no digestive symptoms, and was only given a test-meal because she had told me that her sister had died from Addison's anæmia, was also found to have achlorhydria. I have collected records of thirteen other cases in which Addison's anæmia in one or more members of a family was associated with achylia gastrica in others. (Table II (d)). One of the most remarkable instances is the family described by Weinberg, in which a man with Addison's anæmia had four healthy children, three of whom, aged respectively 10, 6 and 4, had, like their father, complete achylia gastrica.

TABLE III.—HISTORY OF ACHYLIA GASTRICA PRECEDING ONSET OF SYMPTOMS OF ADDISON'S ANÆMIA OR SUBACUTE COMBINED DEGENERATION OF THE CORD.

Disease	Number of years	Author
A.'s a. ..	13, 10, 7, 3 ..	Faber.
A.'s a. ..	12 ..	Bie.
A.'s a. ..	7 ..	Cobet and Morawitz.
A.'s a. ..	5 ..	Kuttner.
A.'s a. ..	2 ..	Chas. Hunter.
A.'s a. ..	6, 1 ..	Levine and Ladd.
A.'s a. ..	10, 3 ..	Wilkinson.
A.'s a. ..	8 ..	Weinberg.
S.C.D. ..	1	Wilkinson.
S.C.D. ..	2 ..	Szlapka.

Eight cases have been recorded in which achylia gastrica was discovered from one to thirteen years before the onset of symptoms of anæmia (Table III). Dr. J. F. Wilkinson, of Melbourne, has observed one case and Szlapka has recorded another, in which achylia was known to be present for one and two years respectively before the first symptoms of subacute combined degeneration of the cord developed. Pre-existing achylia gastrica is also the probable explanation of the fact that it is very common for digestive symptoms, especially recurrent diarrhœa or nausea, to precede the onset of symptoms both of Addison's anæmia and also, as Farquhar Buzzard in 1910 and Collier in 1921 had pointed out, of subacute combined degeneration of the cord.

(*b*) *Secondary Achylia Gastrica.*

I have seen two cases, and Roth has observed another, in which Addison's anæmia was associated with achlorhydria, which was apparently the result of chronic alcoholic gastritis, as cirrhosis of the liver was present. Typical Addison's anæmia has also been observed in patients with cancer of the stomach, in which no secondary deposits in the bone marrow were found after death. In the four cases recorded by Brandes, and in the only one of the kind I have seen complete achylia gastrica was present.

In 1922, when we published our paper in *Brain*, Bell and I had failed to discover the report of any case of cancer of the stomach associated with subacute combined degeneration of the cord, although several writers had referred to the occurrence of such an association. We suggested that, should future observations prove the existence of this association, it would probably be found only to occur among the 60 per cent. of cases of cancer of the stomach in which complete achlorhydria is present throughout the period of digestion. In the following case, which came under my care almost immediately afterwards, as well as one still more recently recorded by Garvey and Stern [2], our prediction was fulfilled.

Subacute combined degeneration of the spinal cord with Addison's anæmia secondary to cancer of the stomach.—A man, aged 52, was admitted in August, 1922, for progressive weakness of the legs and arms and pains in the chest and abdomen. In October, 1921, he had begun to have a sensation of "pins and needles" in his hands and forearms, and he found that his limbs were getting weak. In December indigestion appeared with pain from one and a half to two hours after meals. He vomited occasionally and twice noticed a little blood in the vomited material.

In June, 1922, the weakness and "pins and needles," which had been almost confined to the upper limbs, appeared in his feet and legs. There was also some unsteadiness in walking. He found that exertion gave him pain in the region of his heart and made him short of breath. Between June and his admission in August his weakness became more marked, and for some months he steadily lost weight. Since March, 1922, his tongue has been painful and ulcerated.

On admission the patient's complexion was a pale lemon-yellow colour. His cranial nerves showed no abnormality. His knee-jerks and ankle-jerks were normal and equal: the plantar reflexes were extensor. The abdominal reflexes were difficult to obtain. Vibration sense was absent in the left leg and diminished in the right. There was some loss of muscle sense in the right fingers and left toes. There was no astereognosis. The patient could differentiate hot from cold, but pin-pricks and the touch of a blunt object on the

fingers seemed to him the same. He was able to appreciate the touch of cotton wool everywhere except on the soles of his feet. His muscles were flabby and feeble, but his grip was fairly strong. The blood and cerebrospinal fluid gave negative Wassermann reactions, and the latter contained no excess of cells.

His tongue was fissured and sore, all filiform papillæ had disappeared, and several small ulcers were present. There was universal severe pyorrhœa alveolaris. The tonsils were normal.

A fractional test-meal showed complete achlorhydria with blood, pus and mucus in each specimen; the gastric contents had a very foul smell. The X-rays showed a hypertonic rapidly emptying stomach with no irregularity in outline. The fæces gave a strong guaiac test and a well-marked hæmatoporphyrin spectrum. A doubtful tumour was felt high up in the epigastrium. The spleen was enlarged and firm. The liver was slightly enlarged. The urine was dark in colour, but contained no abnormal constituents. The bowels were regular. The systolic blood-pressure was 88 mm. and the diastolic 55 mm. Hg. The heart was normal.

The red corpuscles numbered 1,500,000 per c.mm., and the hæmoglobin percentage was 31, the colour index being thus 1·03; the leucocytes numbered only 4,700 per c.mm. Dr. Price-Jones reported that the blood film presented the typical picture of Addison's anæmia. Van den Bergh's test gave a negative direct and a positive indirect reaction.

A diagnosis of subacute combined degeneration of the cord with Addison's anæmia and hæmorrhagic gastritis or possibly carcinoma of the stomach was made. As no improvement followed removal of the septic foci in the mouth, the administration of hydrochloric acid and arsenic, and transfusion repeated on three occasions, Mr. R. P. Rowlands was asked to operate on October 24 in order to remove the spleen if no growth was found. A large inoperable growth was, however, discovered in the cardiac half of the stomach with large and hard glands near the lesser curvature, and there was pus in the peritoneal cavity. The patient died ten days later.

At the post-mortem the heart was surrounded by a great deal of bright yellow fat. The stomach showed a large fungating mass occupying more than half of the mucous surface. Many hard glands were found along the greater and lesser curvatures. The liver had one nodular lump on its surface, and the pancreas contained several secondary deposits. The spleen was soft and enlarged, 18 cm. long, with its capsule thickened. The ribs on section showed an extraordinary development of the red marrow. Dr. C. P. Symonds found the typical changes of subacute combined degeneration in the spinal cord.

In the case recorded by Garvey and Stern [2], typical subacute combined degeneration of the cord was present in a patient with a lemon-yellow colour, complete achlorhydria caused by cancer of the stomach, and slight anæmia with a high-colour index; the red corpuscles numbered 3,150,000 per c.mm., the hæmoglobin percentage was 81, and the leucocytes numbered 5,100 per c.mm. The onset of ner-

vous symptoms preceded the gastric symptoms by ten weeks, but by the time they appeared the malignant disease was already advanced.

The complete achylia which results from gastrectomy performed for cancer of the stomach may be followed by the development of Addison's anæmia (Hartman, Moynihan), and Ellis has recently described a case of subacute combined degeneration of the cord associated with Addison's anæmia, in which the first symptoms appeared seventeen years after the performance of gastrectomy.

Lastly, the achlorhydria, which often follows gastro-enterostomy owing to the neutralization of the gastric contents by the alkaline juices of the duodenum and the rapid drainage of the stomach, has in rare instances been the precursor of Addison's anæmia (Campbell and Conybeare; Willcox).

Oral Streptococcal Infection.

In the absence of the germicidal barrier, which is normally formed by the free hydrochloric acid of the gastric juice, even a slight degree of oral sepsis becomes a dangerous source of intestinal infection. In the majority of cases of Addison's anæmia and subacute combined degeneration of the cord obvious pyorrhœa alveolaris is present. In the remaining cases expert clinical and radiological examination has, in my experience, always revealed the presence of definite periodontal infection, except when the patients were edentulous. The existence of these diseases in patients who had lost all their teeth, sometimes several years earlier, has been used as an argument that oral sepsis plays no part in their pathogenesis. But the teeth must have been extracted because at an earlier period dental sepsis was present, and its eradication may have been too late to prevent the development of secondary infective foci, which ultimately caused the disease, though sometimes not until several years later. Thus in two cases, in which the patients had been edentulous for six months and five years respectively, radiograms of the jaws showed areas of rarefying osteitis, in which long streptococci were found to be still present. Occasionally the tonsils and very rarely the nasal sinuses are sources of infection, both in edentulous patients and in patients with septic teeth.

Only second in importance to the teeth is the tongue, which, as William Hunter first showed twenty-five years ago, is almost invariably the seat of a chronic streptococcal inflammation in Addison's anæmia. Since I learnt how to recognize the slighter forms of this Hunterian glossitis, which is characterized by the complete disap-

pearances of all filiform papillæ, and which is often present without any complaint of soreness, I have found it in almost every case of subacute combined degeneration of the cord as well as of Addison's anæmia. Not infrequently patients give a history of sore tongue preceding any symptoms due to anæmia or nervous disease, and I have now twice been able to recognize Addison's anæmia in a very early stage in patients who were sent to me solely on account of glossitis. It is clear, therefore, that the tongue may be a secondary source of infection even after the removal of all septic teeth.

Lastly, there is no reason why intestinal infection may not remain latent for years after the disappearance of the primary infective focus in the mouth; an incidental attack of food poisoning may so affect their chemical environment that the hitherto harmless streptococci may develop hæmotoxic and neurotoxic properties.

Further evidence of the connection between oral sepsis and subacute combined degeneration of the cord is the frequency with which patients complain of a slight and temporary increase in the tingling of their feet and hands about twelve hours after a tooth has been extracted or after a vaccine made from dental streptococci has been administered. Extraction of several teeth without preliminary vaccination and over-doses of vaccine may give rise to permanent aggravation of symptoms.

F. A. Knott [4] has shown that free hydrochloric acid in a strength considerably less than that found in the average normal stomach is sufficient to destroy many forms of bacteria, but especially streptococci. In normal individuals the duodenum is consequently either sterile or it contains a few bacteria of various kinds, but rarely any streptococci. In achlorhydria the number of bacteria is greatly increased, but it is a curious fact that even in the presence of oral sepsis streptococci are uncommon, except in patients with Addison's anæmia and subacute combined degeneration of the cord. In our earlier paper Bell and I could only refer to eleven cases of these diseases and twenty-six controls; I am now able to give figures relating to twenty-eight cases of Addison's anæmia and twelve of subacute combined degeneration of the cord to compare with 145 controls (Table IV).

In 77·5 per cent. of the former *S. longus* was found, compared with 20 per cent. of the controls. In many of the latter they were scanty and slow growing. In four of the seven cases of Addison's anæmia, and in one of the two cases of subacute combined degeneration of the cord in which streptococci were not isolated from the duodenal contents,

large doses of hydrochloric acid had previously been given. As in several instances we have found that the *S. longus* present in the duodenum when first looked for disappeared at a second examination after treatment with hydrochloric acid, it is not unlikely that streptococci would have been found in these five cases if the examination had been made before any acid had been given.

TABLE IV.—*Streptococcus longus* IN DUODENAL CONTENTS.

(a) *By duodenal intubation (Lemnos, New Lodge Clinic, Guy's Hospital).*

Disease	Number examined	Number present	Percentage	Notes	Bacteriologist
Normal	4	0	0	When found, generally very scanty and slow growing. *In 19 with achlorhydria no streptococci found.*	C. J. Martin
Infective jaundice ..	8	0	0 · 20		C. J. Martin
Various diseases ..	133	29	21·8		F. A. Knott
Addison's anæmia ...	28	21	75 · 77·5	In 4 of the 7 A.'s a. and in 1 of the 2 S.C.D. with no streptococci large doses of HCl had previously been given.	F. A. Knott and R. D. Passey
S.C.D. of cord ..	12	10	83		

(b) *By direct puncture during abdominal operation (Guy's Hospital).*

Cholecystitis, duodenal ulcer, chronic appendicitis, and megacolon	5	0	0	2 sterile; 2 a few *B. coli*; 1 a few *Staph. alb.*	W. H. Ogilvie and F. A. Knott
Addison's anæmia ..	2	2	100	Fairly abundant, hæmolytic in one; very few, non-hæmolytic, in other.	F. A. Knott A. Stokes

In seventeen out of nineteen cases of Addison's anæmia and subacute combined degeneration of the cord, in which the question was investigated, the duodenal streptococcus was found by Knott to be hæmolytic. It is an interesting fact that the two exceptions were both cases of subacute combined degeneration of the cord, one being the only case in which no anæmia was present, the other being one in which the anæmia was slight. In five out of twenty cases of other diseases in which streptococci were found, they had hæmolytic properties; this is about the same proportion as in the streptococci normally found in the mouth.

In a series of six cases of subacute combined degeneration of the

cord investigated by Worster-Drought, streptococci were isolated from the duodenal contents of all, and in five of the six the streptococci were hæmolytic.

The Intestinal Toxins.

In our former paper we suggested that the streptococcal infection led to the production of a hæmolytic toxin and a neurotoxin. It would probably be more correct to speak of hæmotoxins and a neurotoxin, as the form of anæmia called Addison's (or pernicious) anæmia owes its specific hæmatological characters to a toxin which acts directly upon the bone marrow in addition to a hæmolysin. Hæmolytic anæmia is not necessarily Addisonian, Addison's anæmia being not merely a hæmolytic anæmia, but a hæmolytic anæmia associated with an increase in the average size of the red corpuscles, which occurs in no other condition except sprue and *Bothriocephalus* infection. The macroblastic activity of the bone-marrow does not depend upon the hæmolysis, as it is recognizable in patients with subacute combined degeneration of the cord and with Hunterian glossitis before any anæmia has developed, and it persists in most cases of Addison's anæmia during prolonged remissions, in which the patient appears to be perfectly well and in which pathological hæmolysis has completely ceased, as shown by the disappearance of the lemon-yellow colour and by the negative Van den Bergh's reaction of the blood. The anæmia, lemon-yellow colour and characteristic Van den Bergh's reaction (negative or delayed direct, positive indirect) are the direct results of hæmolysis. The microcytes, poikilocytes, micro- and normoblasts, polychromasia and punctate basophilia are due to the normal reaction of the bone marrow to any form of anæmia, so that these features of the blood picture may appear in hæmorrhagic anæmia and to a still greater extent in all forms of hæmolytic anæmia. But the average increase in the size of the red corpuscles with the consequent increase in the colour index and the occasional presence of megaloblasts are the result of a specific toxic action on the bone marrow. The association of microcytes and macrocytes is the cause of the extreme degree of anisocytosis which is present. The doubt which has hitherto been expressed by many authors as to the nature of the anæmia associated with subacute combined degeneration of the cord is due to the fact that most pathologists have been unwilling to diagnose Addison's anæmia until the complete blood picture is present. The work of Price-Jones [5] has, however, shown conclusively that the increase in the average size

of the red corpuscles is the one essential characteristic feature of the blood picture, and that it may occur alone in the early stages of the disease.

With our present knowledge there can no longer be any doubt that the anæmia in subacute combined degeneration of the cord is always of the Addisonian type. The early stages of the anæmia, in which a diagnosis is rarely made in uncomplicated cases, is that which is most frequently present when a case of subacute combined degeneration of the cord first

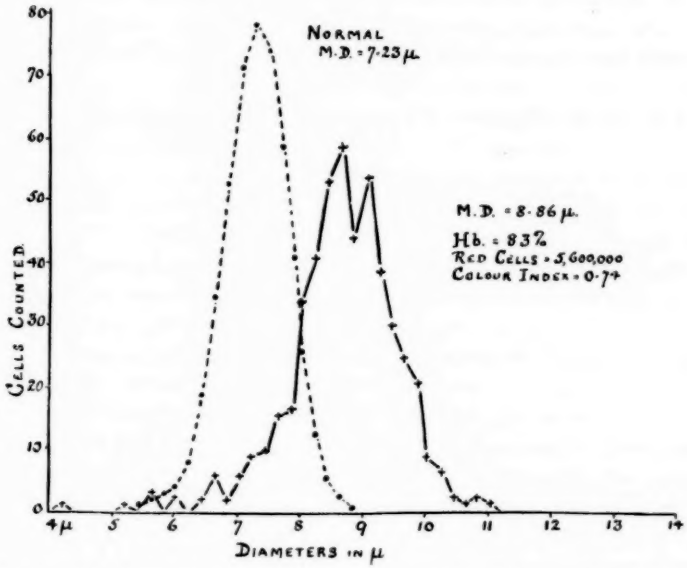


FIG. 1.—Price-Jones curve in a case of subacute combined degeneration of the cord without anæmia, but with the typical megalocytosis and anisocytosis of Addison's anæmia. Complete achlorhydria was present. The dotted curve is a chart of the sizes of 10,000 red cells from twenty healthy persons, with a mean diameter of 7·23 μ; the irregular curve is a chart of the sizes of 500 cells from the S.C.D. case with a mean diameter of 8·86 μ. (A. C. Hampson and J. W. Shackle).

comes under observation; the colour index is then sometimes under 1 and nucleated red corpuscles are rarely seen. In all of our cases, however, and even in two with a red corpuscle count of 5,300,000 and 5,600,000 respectively per cubic millimetre, megalocytosis was present, and the Price-Jones curve was typical of Addison's anæmia whenever it was charted (fig. 1). In most cases the blood-serum was abnormally pigmented, and Van den Bergh's indirect reaction for bilirubin was positive, the direct reaction being negative or delayed. But in three early cases, including

the two just mentioned, this evidence of hæmolysis was absent, but the megalocytosis showed the true Addisonian character of the anæmia. As active treatment was at once instituted, it may be hoped that a hæmolysin will never be formed in sufficient quantity to cause anæmia and that the formation of a neurotoxin will be permanently arrested.

Prophylaxis and Early Treatment.

As everybody with achlorhydria can be regarded as liable under certain conditions to develop Addison's anæmia or subacute combined degeneration of the cord, whenever the former is discovered in the course of a routine investigation of a patient suffering from digestive or other symptoms, he should be advised to take hydrochloric acid in adequate doses for the rest of his life. At the same time all oral sepsis should be eradicated, and the patient should be instructed to have his teeth thoroughly examined and treated every six months. This will not only probably make him safe so far as Addison's anæmia and spinal degeneration are concerned, but also cure any digestive symptoms, such as nausea or chronic diarrhœa, which may be present, and diminish the special liability he has to develop such conditions as rheumatoid arthritis, appendicitis, cholecystitis and acne rosacea.

Familial Addison's anæmia is due to familial achylia. It is, therefore, worth considering whether it would not be wise to examine the gastric contents of the other members of the family of patients with the disease (*vide* Table II (d)), and, if achylia is found, advise them to take the precautions I have just described.

The prospect of eradicating the infection which causes Addison's anæmia and subacute combined dageneration of the cord is, of course, much more favourable in early cases than when the disease is well established. Early diagnosis can only be made if in every case in which achlorhydria is discovered, in every case of sore tongue or of recurrent glossitis, and in every case of paræsthesia affecting the feet and hands, a thorough examination of the blood and central nervous system is made, and in the two latter conditions a test-meal is given. It should be remembered that the examination of a blood-film for megalocytosis is far more likely to lead to an early diagnosis than a simple blood count and hæmoglobin estimation, and that the criteria upon which many hæmatologists depend for a diagnosis of Addison's anæmia are only present in the more advanced stages when treatment is much less hopeful. It should be remembered also that in subacute combined degeneration of the cord with achlorhydria but normal blood, early treatment can be

regarded as prophylaxis of Addison's anæmia, which is otherwise almost certain sooner or later to develop.

Treatment.

The treatment described in our former paper requires amplification in certain directions. The removal of several septic teeth at one time may lead to the absorption of such a large dose of toxin that an acute hæmolytic or neurolytic crisis may result. The former is not very serious, as the anæmia can later be overcome by treatment with arsenic, and, if necessary, repeated transfusions. On the other hand an acute aggravation of the nervous condition is to a great extent irreparable. It is therefore essential to do everything possible to prevent the occurrence of such crises. A single tooth should be removed in the first instance, and a vaccine should be prepared from the streptococci isolated from it. Two or three doses of this should be administered at intervals of five days, and then, five days later, not more than two or three of the infected teeth should be extracted. The remainder should be removed at intervals of a week, the number at each sitting depending upon whether any reaction followed the earlier extractions.

In edentulous patients the jaws should be X-rayed, and any areas of rarefying osteitis which are discovered should be scraped and disinfected.

Knott has shown that hydrochloric acid loses its antiseptic properties when combined with proteins, although it is still able to activate pepsin. Hence it is best to give the first dose of acid when the stomach is empty an hour before breakfast, the other doses being taken immediately before and during lunch and dinner. Most patients can take the full dose of two drachms which we find is required to compensate for the complete achylia, but it is sometimes necessary to begin with one drachm and slowly increase the dose. When diluted to a strength of one drachm to four or five ounces of water, with the addition of the juice and pulp of an orange and sugar, few people raise any objection to continuing with it, as they should do, for the rest of their lives, even during complete remissions.

For patients who dislike sour milk, two drachms of a culture of *B. acidophilus* can be substituted, as it appears to act with equal efficiency. A tablespoonful of powdered animal charcoal taken morning and evening is also useful in helping to overcome the intestinal toxæmia.

If a long streptococcus is isolated from the duodenal contents a

vaccine should be prepared from it and given in slowly increasing doses for a long period. If no duodenal streptococcus is isolated, a vaccine should be prepared from a streptococcus obtained from the teeth, tonsils or other infective focus, especially if one with hæmolytic properties is found.

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A CLINICAL STUDY OF SENSORY JACKSONIAN FITS.

BY OTTO SITTIG, M.D. (PRAGUE).

CLINICAL investigation has two aims, a practical and a scientific one. The former is the diagnosis of disease by induction; the latter is the inference from the pathological symptoms to physiological processes by empirically determined facts and by conclusions drawn from them. Observations, which are the basis of all natural science, need constant control, and the correctness of the inferences drawn from them must be continually examined.

This method might be termed "clinical dialectics," and Hughlings Jackson was a master of it. Scarcely anybody has recognized the essential nature of that method as clearly as Jackson himself. This clearness of thought was one of his most admirable qualities. In one of his clinical lectures Jackson started with the following quotation from Lord Bacon: "It is easier to evolve truth from error than from confusion." This sentence might be the motto of the whole of Hughlings Jackson's work.

He drew special attention to one mistake in applying this method. In making conclusions all symptoms must be regarded, even the most minute, the apparently least; nothing must be omitted for the sake of any hypothesis; the inferences must be made in such a way that they can explain all symptoms, even the slightest. On this occasion Jackson quoted a sentence from Curnow: "The tendency to appear exact by disregarding complexity is an old failing in medical history."

No one has so fully recognized the great importance of this fact as Arnold Pick. He has repeatedly insisted that it is slight or trivial symptoms, which are often disregarded as they do not fit easily into a scheme, that frequently throw most light on physiological or pathological problems.

An attempt to apply this method is made in the following paper, which therefore may be devoted to the memory of Hughlings Jackson and Arnold Pick.

It is well known that Hughlings Jackson was the first to direct attention to epileptic convulsions beginning unilaterally (in the face,

hand or foot); he assumed them to be caused by local discharges of a part of the grey matter. Later this hypothesis was verified by the famous experiments of Fritsch and Hitzig. Our knowledge of the motor "centres" has since been more advanced, especially by Sherrington and his school.

After the discovery of Jacksonian motor fits, the so-called "sensory Jacksonian fits," or attacks of paræsthesiæ occurring spasmodically in a certain part of the body and spreading in a certain order, were described. It is not generally known who first used the term "sensory Jacksonian fits." According to Arnold Pick, whose intimate knowledge of the history of neurology and psychiatry is well known, this term was first employed by Krafft-Ebing in describing sensory paralytic attacks in his book on General Paralysis.

We know from the researches of Cushing [1] and van Valkenburg [30], who excited electrically the cortex of the post-central convolution in men who had been trephined without narcosis, that there are in the gyrus centralis posterior sensory "centres" arranged in an order analogous to that of the motor points in the gyrus centralis anterior. The electrical irritation of these points in the post-central convolution produces paræsthesiæ in certain parts of the body.

In sensory Jacksonian fits the patients do not lose consciousness, and therefore we can obtain from them more precise and accurate information on the distribution of the paræsthesiæ than it is possible to secure in motor epileptic convulsions. In the latter the patients usually become unconscious early, and owing to the rapidity of the spread of the convulsions it is often impossible to determine precisely the succession of the muscles involved in the epileptic attack.

My teacher, Arnold Pick, indeed used to emphasize the great value of subjective phenomena in nervous disease. I have consequently directed my attention to subjective sensory disturbances, and by inducing my patients to describe precisely their sensory seizures I have obtained some striking and unexpected observations.

Case 1.—B. J., coppersmith, aged 32. He was struck in 1904 by a hammer on his head, but had no troublesome symptoms afterwards. In 1917 he hurt the same part of his head and was operated upon in Vienna. In January, 1923, he received another blow on the same part of his skull, and after this the first attack occurred. The fit began with formication, or a peculiar, strange abnormal feeling, in the right corner of his mouth (inside and outside, especially the inner surface of the cheek); from here it flashed to his right shoulder, went from there down to his hand, then appeared in his hip and descended to his foot. Then convulsions set in first in the right

corner of his mouth; he tried to fix this part by pressure by his free hand, but it continued to twitch. His right hand then became tight, his fingers spread out and his hand assumed a claw-shape; his arm was over-pronated, so that his palm was turned outwards. He was never unconscious. During the fit he spoke only with difficulty.

After the administration of "Epileptol" at Dresden the attacks got milder. To-day they consist of only a tingling feeling, with no convulsions or twitchings. He complains of severe headaches in the region of the scar, and when this is pressed upon he feels formication in the whole right side of his body. In his right arm and leg he has a feeling of clumsiness and weakness.

Examination on July 5, 1923: The patient is a big, robust man. Over his left parietal bone there is an arcuate scar about 10 cm. long. His lungs and the heart are normal. His pupils are equal and react promptly to light. His ocular movements are well performed; there is no nystagmus. The right corner of his mouth moves a little less well than the left. His tongue is protruded straight; on its right border there are three scars as a result of biting. Sensibility is diminished in the right half of his face, in the region of the second and third branches of the trigeminal nerve. Motility and power are good and equal on both sides. The jerks and other reflexes are normal. The appreciation of touch and pain is diminished on his right arm and leg, but not on his trunk. Deep sensibility and stereognosis are unaffected.

This is a case of traumatic epilepsy with a sensory aura.

Case 2.—H. T., girl, aged 26. In her childhood she had convulsions and scarlet fever, and at 7 years typhoid fever. In September, 1922, the patient vomited frequently, especially on bending forwards, and then became giddy. She had also double vision. Her state soon improved. In February, 1923, she was not able to bring her left leg forward, and had a tremor in her left leg and hand. She dragged her left toes along the ground. Later her right leg became weak too, so that she could not walk. Occasionally there occurred tingling and a feeling of numbness, which began in the right temporal region, passed over the neck and shoulder to her arm and down to the tips of her fingers; then along the trunk down to her toes.

At present the patient complains of severe headaches. Her menses are irregular. She denies venereal infection.

The pupils react promptly to light and convergence. The ocular movements are normal. The abdominal reflexes are abolished on both sides. The left knee-jerk is exaggerated; Babinski's and Oppenheim's signs are present on both sides, and ankle clonus can be elicited on the left. There is no ataxia, but slight intention-tremor. Romberg's sign is present. There is a coarse nystagmus, especially on looking to the right, and temporal atrophy of both discs. Dorsal flexion of the left foot is weaker than of the right. The Wassermann reaction is negative.

This is a case of disseminated sclerosis with attacks of paræsthesiæ.

Case 3.—K. J., woman, aged 51. A year ago she found suddenly that she could not move the toes of her left foot. Then she began to limp and had pains in her left leg up to the hip. The pains disappeared, but she continued to limp. In her knee she had a feeling as if the bones were not in proper apposition. Three times she had attacks of twitching in her legs, especially in the left, each lasting two to five minutes. At the same time she had a feeling of numbness in the left half of her body, which began at her left ear and passed down her neck and shoulder to her arm, sometimes on the radial side to the thumb, sometimes on the ulnar side to the little finger.

On examination: The pupils are equal and react promptly to light. The ocular movements are well performed, and no nystagmus is present. The fundi are normal. The corneal reflexes are diminished. Sensibility is unaffected on the face. The left corner of the mouth is moved a little less well than the right. The abdominal reflexes are present and equal on both sides. The left knee-jerk is brisker than the right. On the left foot Babinski's sign can be obtained. Dorsal and plantar flexion of the left ankle-joint and of toes are impossible and flexion of the hip, knee and inward rotation of her left leg are weaker than on the right. The tone of her left leg is somewhat increased, and it is slightly ataxic in movement.

Sensibility: She feels light touch on her left foot less well than on the right. The appreciation of heat and cold is disturbed on her left foot, heat being perceived as cold. The perception of passive movements is affected in her left big toe.

The cerebrospinal fluid is quite normal.

I saw this case together with Professor Pötzl. We thought at first of a tumour of the spinal cord, but as the symptoms were not progressive, and as the patient described fits involving her face, we were obliged to diagnose multiple lesions, perhaps disseminated sclerosis.

Case 4.—L. D., girl, aged 11. For $4\frac{1}{2}$ years she has had attacks of formication beginning in her left axilla and passing along her arm to her fingers, or over her neck to the left half of her tongue and lips. Sometimes it begins in her left fingers and goes up her arm and neck to the left half of her face. Sometimes it spreads from her left axilla over the trunk and from her hip down to her toes. If it begins in her face it spreads to the left half of her tongue and thence along her neck and arm downward to her fingers. Sometimes it involves only the left half of her tongue and lips, sometimes the whole left half of her body.

At first the attacks occurred rarely; since Christmas, 1923, they are more frequent; in the last week three occurred. She has vomited after the later attacks and they have been followed by severe headache over her forehead. During the attack her vision is misty and she sees black circles before her eyes and looks pale.

The neurological examination revealed nothing abnormal except a slight difference in the abdominal reflexes, the left being feebler than the right.

The attacks in this case are probably of migraine. Arnold Pick has described in an early paper a case of migraine with paræsthesiæ on one side of the face and in the fingers.

Case 5.—G. F., male, aged 42. At the beginning of war the patient hada palsy of the eye-muscles which lasted two years. Later his memory was impaired, his speech became incorrect and he omitted words. In the spring of 1923 he had frequent attacks of suffocation, gasped for breath, was cyanotic and his hands moved. These seizures, of which he has had six, lasted up to half an hour. In them he states he could utter only indistinct sounds.

The patient said he had fits during which his limbs became numb. "It goes from one foot upwards; for instance, it begins in the toes, then it goes up the leg and over the trunk, chiefly to the right fingers; thence up the arm to the neck and to the mouth, the lips, the tongue and the teeth. The latter chatter." Sometimes it may be on the right side, sometimes on the left. The attacks generally start in the evening or in the morning and last ten to fifteen minutes.

Another time he describes such a sensory fit as follows: "It begins in the left toes and passes up to the face; then it goes to the other side of the face, down the arm on its outer side from the shoulder to the fingers, then to the inner side of the arm from the fingers to the shoulder back again, and finally over the trunk to the leg."

A third time he described the attacks in these words: "It begins in the tips of the fingers, goes to the shoulder and the side of my head; my teeth and lips become numb. (He points with his hand from the forehead to the cheek. Then he indicates the right half of his trunk, the front side of his leg to his toes, then the posterior aspect of his leg upwards to his back.) Finally it spreads to the other half of the body."

Sometimes the attack begins in his toes, sometimes in his fingers, but never in his face.

His pupils are unequal, the left being wider than the right. The left pupil does not react to light at all, the right only partially. The reaction to convergence is less in the left than in the right. The ocular movements are well performed, but there is nystagmus on looking to the right side. In speaking the left corner of the mouth is moved less than the right, and the facial muscles tremble as he talks. His speech is slow, indistinct, monotonous and blundering. The Wassermann reaction of his blood and of the cerebrospinal fluid is ++++, and there are 33 cells per c.mm. in the latter. The gold-sol reaction is that of general paralysis.

Case 6.—K. H., male, aged 43. General paralysis; demented and euphoric in behaviour. His gait is unsteady, his speech slow and indistinct. His pupillary reflexes to light are feeble. The Wassermann reaction is positive in both his blood and cerebrospinal fluid; the other reactions are positive too.

The patient said he suffers with fits beginning with a glimmering before his eyes. Then occurs a tingling in his fingers, mostly on the left, which goes up his arm to his shoulder, flashes across his neck and his cheek, and ascends

directly to his tongue. At other times the patient said it begins usually in his toes, mounting up his leg, and after ceasing in his leg it appears in his fingers.

The attacks affect the left side and the glimmer is also to the left. During the attacks he had headaches, but never convulsions. The left corner of his mouth was involved at the same time as his tongue; then he could not speak. The patient said he was right-handed.

The patients 5 and 6 are cases of general paralysis with sensory fits.

Case 7.—O. M., girl, aged 21. The patient has suffered with epileptic seizures for five years; typical attacks were observed in our clinic, with biting of the tongue and inactivity of the pupils to light. She has two kinds of attacks, severe and slight ones. All begin with paræsthesiæ in the fingers of her right hand. In the severe ones there follow unconsciousness and then convulsions. In the slight attacks the patient does not lose consciousness and there are no spasms.

The march of the paræsthesiæ she describes as follows: In each fit she feels first a tingling in her right fingers, which goes up her right arm to her shoulder, then over her neck to the right side of her face, head and tongue. Sometimes it begins in the right side of her face, either at the angle of her mouth or in the temporal region, and passes over her neck to her shoulder and down her arm to her fingers. Sometimes it spreads from her hand to her shoulder, neck and face, then to the right half of her trunk and to her leg; or from her face to her arm and simultaneously to her trunk and leg. Sometimes when the paræsthesiæ affect her face she turns her eyes to the right and screws up the lids of her right eye.

This is a case of epilepsy with a sensory warning.

Case 8.—L. W., man, aged 26. On July 1, 1924, the patient, who had been hitherto in good health, had his first attack one night on being awakened suddenly by his mother. The seizure began with a "dead" feeling in the tips of his right fingers, which spread to his arm and to the right half of his face and tongue. Simultaneously with the onset of the paræsthesiæ his right arm flexed at the elbow and his mouth and jaw were drawn to the right. He said he was unable to speak during the fit, but able to think.

As long as he remained conscious he felt as if he were drawn to the right and would fall forwards. In some seizures he lost consciousness and sometimes he bit his tongue.

The Wassermann reaction was negative in his blood. He had no headache, vomiting or vertigo. In speaking he showed slight weakness of the right angle of his mouth. Otherwise there were no abnormal signs; his fundi were also natural.

The case was probably one of epilepsy like Case 7.

Case 9.—B. J., boy, aged 13, had attacks for two years following a nephritis. Three months before the third seizure he was thrown by a friend on to the rails, striking his right temple and losing consciousness for ten minutes.

The fits he describes as follows: Half an hour before they begin he has a headache, always on the opposite side. The seizures sometimes involve the right side, sometimes the left. They always begin with formication in all the toes of one foot, which ascends his leg to the hip, flashes to his fingers and goes up his arm, and simultaneously it passes up his trunk from the hip. Then it crosses his neck to the same side of his face, nose and eye, and to one half of his tongue. When it affects his tongue he cannot speak. It may be on the right or on the left. He says he understands speech but uses incorrect words, or cannot utter certain sounds. When it reaches his eye his sight is blurred or objects seen seem to move from side to side. During the attack the side involved is cold. He has no convulsions and he does not lose consciousness. After the fits, which last generally for an hour, he has severe headaches and he becomes sleepy. The paræsthesiæ pass off slowly, first from the toes, in the same order as they came on. He has attacks at intervals of a fortnight, a month or two months.

The right corner of his mouth moves a little less than the left. The fundi are normal. He has an orthostatic albuminuria and his capillaries show angioneurotic changes.

Probably in this case the fits are attacks of migraine with sensory phenomena like those in Case 4.

Case 10.—P.A., male, aged 26. Since 1919 he has had convulsions of the right half of his body. The fits begin with paræsthesiæ in his fingers, which pass over his arm to his shoulder, then over his neck to the right half of his face, and finally down his trunk into his right leg. Then his right arm is flexed tonically, his mouth is drawn to the right and he loses the power of speech. A neurological examination revealed nothing abnormal.

This is probably a case of epilepsy.

The common feature in these ten cases is that there occurred in each of them attacks of paræsthesiæ which may be regarded as sensory Jacksonian fits. These paræsthesiæ commenced in a certain part of the body and spread in a certain order. The anatomical basis of these attacks is generally assumed, in analogy to cortical epileptic motor attacks, to be an excitation of the post-central convolution, which starts from a certain point and spreads to the neighbouring cortex. It is therefore usually believed that the spread of the paræsthesiæ over the body is determined only by the arrangement of the sensory areas in the gyrus centralis posterior. The localization of these sensory points in this convolution corresponds to that of the motor spots in the precentral gyrus.

If sensory Jacksonian fits were determined by the arrangement of the sensory foci, the march of paræsthesiæ commencing at the toes

would be upwards over the leg to the hip, hence to the shoulder, along the arm to the fingers, then to the face.

There were, however, considerable divergencies from this order in some of my cases.

(1) From the face to the shoulder along the neck, or, omitting the neck, along the arm to the fingers, then along the trunk, or omitting it, to the hip and hence to the toes (Cases 1, 2, 3, 4, 7).

(2) From the shoulder to the face, not affecting the neck (Case 4).

(3) From the fingers or the hand to the shoulder, and then over the neck to the face (Cases 5, 6, 7, 8, 10).

(4) From the shoulder over the trunk to the hip, and thence down the leg to the toes (Case 4).

(5) From the toes to the hip, then to the trunk, and from the fingers up the arm and into the face (Cases 5, 6, 9).

The striking feature of these observations is that the paræsthesiæ spread from the arm to the face or inversely, or that they jumped from the hip to the fingers and passed up the arm to the shoulder.

The sequence does not therefore correspond to the order of the sensory points in the gyrus centralis posterior as far as we know it; the centres of the fingers, especially that of the thumb, lie in juxtaposition to those of the face, while those for the shoulder are remote from it.

There are clinical observations from which we may conclude that the above-mentioned is the order of the sensory points. I have had myself [27] [28] repeatedly the opportunity of observing paræsthesiæ in the fingers followed immediately by such in the face, and I have particularly noted paræsthesiæ in the thumb followed immediately by subjective sensations in the corner of the mouth, or inversely. And this march is in exact accordance with the experimental findings of van Valkenburg [30]. In one of my cases [27] (D. R.), in which there was probably a circumscribed syphilitic meningitis, there occurred paroxysmal paræsthesiæ on the dorsal aspect of the hand between the left thumb and index finger, and at the same time at the left half of the upper lip. The paræsthesiæ apparently spread no further.

A second case of mine [27] (W. W.) was a paralytic who described sensory fits beginning with formication in the right half of his face, especially in the region of the mouth, in the right half of his tongue, and in his right hand up to the wrist. Another time he felt tingling at the right corner of his mouth, in the side of his tongue, then in his thumb, and later in the other fingers, from where it would wander like ants up his forearm.

Similar observations have been published by other authors. In two earlier papers by Arnold Pick I have found records of this typical localization of paræsthesiæ to the face and hand of the same side. In the one paper [17] he recorded the following case: "On September 19, while knitting, the patient suddenly rubbed her right hand, complaining of numbness of it, and of a similar sensation in her mouth." A second patient [18], who suffered with migraine, described her paræsthesiæ as follows: "Suddenly I feel my left hand all pins and needles, and in my forearm, hand and ulnar fingers a sensation as if the ulnar nerve had been struck, but no pain; at the same time the left half of my upper lip and my left cheek became insensible."

Russel and Horsley [25] described a case of subcortical tumour of the right parietal region in which the patient had "sensory fits," i.e., an aura commencing with a sensation of pins and needles in the third and fourth fingers of the left hand, spreading to the arm, face, trunk and leg of the same side, followed some weeks later by Jacksonian fits starting in the left side of the mouth, which spread to the arm and leg of same side.

Fedor Krause [14] describes a case (his observation, I, 5) of Jacksonian fits predominantly of the sensory variety. Operation revealed a fibrosarcoma of the central region, which was extirpated and the patient recovered. The fits were described as follows: "They began with a dryness of his mouth and a strange sensation (feeling of vibration, numbness, insensibility or tightness) of the left side of his mouth, his upper lip, the side of his nose, and of his tongue. More rarely there occurred a visible vibrating in the left half of his tongue and in the corner of his mouth; the patient could use these parts during the fit. Then appeared a feeling of numbness in the fingers of his left hand, which began in his thumb and spread, after some seconds, to each finger in succession from the index to the fifth finger, then involved the inner aspect of his palm, and either ceased at the wrist or passed up the forearm to the upper arm and ended in the lateral region of his neck."

Van Valkenburg [30] describes three cases of epilepsy with sensory auræ: (1) "Paræsthesiæ (a feeling of tightness, an inward drawing up or tingling) of the whole left arm, sometimes extending to the junction of the shoulder and the trunk. It began regularly in the fifth finger and on the ulnar aspect of the left hand, thence it spread to his arm, or before this over his whole hand. More rarely there occurred contemporaneously with the spread of the paræsthesiæ to the arm a

feeling of tingling in the left half of his face; from the left half of his upper lip it irradiated over the middle of his cheek to his left eyelids." (2) (*a*) Tingling at the right corner of the mouth which spread obliquely over the cheek to the outer corner of the eye; (*b*) The same feeling extending from the right hand along the radial aspect of the arm to the shoulder; (*c*) The same feeling in the whole of the right leg. (3) Tingling on the flexor surface of the end phalanx of the right thumb, instantly followed by paræsthesiæ between the right corner of the mouth and the right eye. In other attacks the paræsthesiæ spread from the right thumb over the whole hand without involving the face.

In Schuster's [26] case, where there was an endothelioma of the post-central convolution and supramarginal gyrus, there occurred occasionally attacks of numbness in the left upper lip and tingling in the left hand and fingers.

Gamper's [6] case, in which there was a bullet wound of the skull, had irritative sensory symptoms in the one half of the face and in the ulnar part of the hand and fingers.

E. Popper [19, 20] has described a case with paræsthesiæ beginning in the tips of the four ulnar fingers, which spread to the hand and the forearm.

M. Löwy [16] has published a case of tumour of the brain in which the following varieties of sensory fits occurred: paræsthesiæ in the tips of all fingers of the right hand and of the thumb, which spread over the fingers and hand up to the middle of the forearm. After some minutes there occurred a momentary feeling of a cold breath of wind on the right cheek. A second variety commenced with tingling in the right half of the face and simultaneously in the right occipital region; the tingling then appeared in the tips of all the right fingers and of the thumb, spread up the hand to the middle of the forearm, thence, "like a contraction," to the right hip and down the right leg.

Sometimes only very limited paræsthesiæ occur, either as an aura of an epileptic attack or as a sensory fit.

A case of mine [28] had right-sided cortical epileptic seizures, commencing with tingling in the right upper lip and in the right half of the tongue. On operation there were found two small gummata in the inferior parts of the post- and pre-central convolutions.

In a case demonstrated by Pötzl [22] cortical epileptic attacks began with formication in the left thumb and index finger, which then spread directly to the left cheek. After trephining the fits commenced with a cutting pain at the left ear, and a similar feeling in the

operation scar; then paræsthesiæ appeared in the left thumb and index finger.

Two cases suffered with fits of both kinds which are here described. The one of these is the above-mentioned case published by Popper [19, 20]. In addition to attacks consisting of paræsthesiæ in the tips of the fingers, there were sensory attacks which occurred alone or as an aura of motor epileptic seizures. In these there was always at first a feeling of cold in the left arm, which spread over the whole limb downwards on to the trunk and then up the body again to the head. At other times the patient had a severe pain in the whole left side. A spasm-like pain would begin in her hand, pass up her arm to her trunk, down the leg to the toes and then upwards again to her head. It was a case of left-sided hemiplegia due to softening.

The second case (L. R.) has been already published by me [27]. It was a boy, aged 15, who had a large nævus on his left forehead. After treatment with carbonic acid snow there occurred obviously a thrombosis of vessels and an extensive softening in the left hemisphere, with epileptic attacks, hemianopia and transitory aphasia. I may quote descriptions which the patient gave of his sensory fits: (April 21, 1914) "At first there was a dazzling blue light, jagged in outline, that went and came again. When I looked at a watch or the wall two blue points came together. Then I had racking pains in my right big toe which spread to the whole foot and then to the arm." The patient said he had often formication in his third, fourth and fifth fingers, followed by a "stiff feeling" in his right upper lip. Sometimes he would have a clumsy feeling in his right upper lip and a strange bad taste on his tongue. On April 26 the patient had an attack which he describes as follows: "It began with flickering in my left eye, followed by a racking pain in my right foot, right upper lip and right hand up to the wrist." Another seizure on April 27 the patient described in the following words: "Yesterday at half past eight I had a flickering in front of my eyes, my right eye became blind but in my left eye the flickering lasted about a quarter of an hour. I threw myself on my bed instantly and my right leg commenced to tremble; this did not last a long time. A spot at the right angle of my mouth became stiff; this occurred three or four times during the afternoon. My hand was affected at the same time as my mouth. I vomited four times and had eructations during the whole day. I had such severe pains that I could have torn myself to pieces."

The patient complained on the next day of a flickering before his

eyes; something blue rising to and fro, and he stated he could not see with his right eye. (There was a right-sided hemianopia.) Then the patient complained of pains in the right corner of his mouth and in his right hand, and his right upper lip became stiff. He continued to rub the latter with his hand, and made movements of chewing and tasting with his lips and tongue. He complained of a disagreeable taste in his mouth. At the same time there were irregular clonic movements of his right leg.

On June 6 the patient complained only of flickering in front of his eyes and stiffness in his right foot. Once the patient said his feet and his lips were stiff.

On June 10, flickering in front of his eyes, stiffness in the right foot, a clumsy feeling in the right arm and on the right side of the nose, the upper lip being unaffected. Sometimes the tingling was present only in his nose; the nose then felt as if obstructed.

On July 7, tingling in his right arm up to his elbow and in his right leg. At the same time the right side of his nose felt swollen.

In two later seizures the patient had paræsthesiæ in the left half of his face.[1]

The records of these cases, and especially the descriptions of sensory fits, are purposely detailed in order to show how variable are their courses. It is obviously incorrect to say that the parts of the body are affected in the order of their representation in the post-central convolution.

That in motor fits, too, the sequence of the spasms does not always correspond to the arrangement of the motor points, seems to be proved by the admirably precise observations of Hughlings Jackson himself. In his "Study of Convulsions" [12] he described a case (5) in which the spasm began with twitchings in the thumb and index finger, followed by flexion of the other fingers and then spasms of the whole arm. Two minutes after the commencement the right half of the face was convulsed. The sequence of the convulsions in this case—thumb and index finger, hand, arm, face—does not correspond to the order of the motor points in the pre-central convolution. It resembled, however, the spread of the paræsthesiæ in some of my own cases. There evidently exists differences in the march of motor spasms analogous to those in sensory fits, but the exact observation of motor attacks is more difficult.

[1] In regard to bilateral sensory Jacksonian fits, see the paper of Löwy and Pötzl, *Medizinische Klinik*, 1924, No. 41. I do not deal with this subject here, as I have no personal observations on this matter.

Hughlings Jackson himself never put forward the view that the march of spasms in epileptiform seizures depends on a spread of excitations (discharges) from one motor centre to adjacent ones; he assumed that the discharge takes place in that part of the cortex where the initial movement is most highly represented, but in which in a less degree all the other parts of the body are represented too. This view agrees with Jackson's conception of the structure and evolution of the nervous system.

In the second of his Croonian Lectures [13] Jackson explains how he thinks the excitation in an epileptic attack spreads. He says: "The point I wish particularly to urge is that not only do those highly unstable cells discharge by 'downward' lines towards the part of the body they especially represent, but that they also discharge laterally by 'cross lines,' and overcome the resistance of healthy, comparatively stable, collateral nervous arrangements of the same general rank, each of which then discharges downwards. Thus partly from the primal discharge, and much more from the secondary discharges of healthy nervous arrangements, there is an enormous energy-liberation towards the periphery."

We may differentiate three groups from the cases described and quoted above. The first includes those in which the sequence of the parts of the body to which paræsthesiæ are referred coincides with the order of the sensory centres in the post-central convolution; in my case L. R., for example, the paræsthesiæ spread from the thumb to the angle of the mouth. But even in such cases there are exceptions; in L. R., for instance, the paræsthesiæ sometimes began in the three ulnar fingers and were succeeded by a feeling of tightness in the upper lip.

The second group contains cases in which the spread of the symptoms does not correspond to the arrangement of the cortical sensory centres. In such patients the sequence of the parts affected may be as follows: face, neck, shoulders, arm, fingers; or big toe, foot, leg, trunk, fingers, arm, face.

As a third group I would place cases in which the paræsthesiæ involve only the radial or ulnar aspect of the arm, or the fore or hind aspect of the leg. In my Case 3 the paræsthesiæ spread down the arm, either on the radial aspect to the thumb, or on the ulnar aspect to the little finger. In Case 5 the patient described paræsthesiæ which sometimes passed down the outer side of his arm and then ascended on its inner side, or descended along the front of the leg and ascended its back. In van Valkenburg's Case 1 [30] the march was

from the little finger to the ulnar aspect of the hand and arm, and in his Case 26 from the hand along the radial side of the arm up to the shoulder. In Gamper's case [6] the paræsthesiæ were referred to the ulnar part of the hand and the ulnar fingers.

Such distributions are well known in cerebral defects of sensation, and are called the pre-axial and the post-axial types. These observations show that not only sensory defects but also paræsthesiæ due to cortical irritations may follow this arrangement.

Another very interesting type may be mentioned. In the case published by Popper [19, 20] some attacks consisted merely of paræsthesiæ in the tips of the fingers, and in my own patient, L. R., paræsthesiæ sometimes appeared simultaneously in his right foot, right hand and right half of his face. This arrangement shows analogy to the distribution of sensory defects, for Goldstein [8] has described a case with slight disturbances of sensation and motion on the right half of the body, in which the corner of the mouth, the thumb and the big toe were the most affected. Goldstein assumed that this was not due to a gross lesion but to damage of the whole region, affecting in greater degree one or other part of it. In order to explain this observation we must suppose that in addition to the local factor there must be a special disturbance of the functionally related centres of the thumb and the great toe.

These facts show that the march of the paræsthesiæ in sensory Jacksonian fits does not always follow the order of the sensory points in the post-central convolution. Hence we must conclude that sensory Jacksonian fits are not simply due to the spread of an excitation along the sensory centres.

These facts agree with the view Hughlings Jackson advanced to explain unilateral epileptic seizures, that there are represented in the part of the cortex in which the initial discharge takes place all those parts of the body involved in the attack as well as that to which the first symptom is referred. I have already mentioned a case described by Jackson [12] himself which shows that in motor seizures the sequence of the parts of the body convulsed does not always correspond accurately with the arrangement of the motor points. This is more easily determined, and therefore more frequently observed, in sensory fits. Such slight and seemingly accidental features are important, since they allow us to make inferences on physiological processes and on the physiological structure of the nervous system.

The supposition here put forward is more strongly supported by the

recent researches of Dusser de Barenne [2, 3]. By his strychnine method, which he applied to the cerebral cortex of the cat and recently to that of the monkey, he found "active zones" in the cortex. In each hemisphere both halves of the body are represented, but the crossed more so. The "active zone" can be divided into zones for the head, the upper limb and the hind limb, which overlap to some extent. The precentral region is included in the "active zone" too. The sensory disturbances increase towards the distal part of the limbs. I may draw special attention to an experiment by this author which seems to me very important; he found that after extirpation of the "active zone" of the one hemisphere and of all that of the other except the point to be stimulated, both sides of the body were involved in contractions. This observation agrees with the famous experiments of Franck and Pitres, often quoted by Hughlings Jackson.

Dusser de Barenne's experimental results also conform with the conclusions that can be drawn from my own clinical material.

There is also a definite accordance between the experimental and clinical observations as to the frequency of the parts of the body first affected in the fits. Hughlings Jackson pointed out that most frequently the warning in motor attacks begins in the thumb and index finger, next passes into the face, then to the big toe. The same course is observed in sensory Jacksonian fits, as the attacks generally begin in the face (lips, corner of the mouth), in the fingers (the tips of the fingers, the thumb and index finger) or in the toes. Less frequently the fit commences in the ulnar fingers, still more rarely in the shoulder (Case 4). If the fit begins in the face the lip or the corner of the mouth is generally first involved; more rarely it commences at the ear (Case 2 and Pötzl's case) or in the temporal region (Cases 2 and 3).

We may now consider the factors which determine this march of the paræsthesiæ. It is noteworthy that this sequence follows the shape of the body. Head supposes that there is a representation or "schema" of the body in the brain. According to his view this is not a fixed or preformed localization, but rather a nervous structure which is especially often thrown in action, a pattern or a frequently employed co-ordinated functional mechanism. Thus it may occur that a stimulus excites or activates with special ease this functional pattern or "schema." That there are still other such functional mechanisms or patterns is well known. Again, it was Hughlings Jackson who advanced such a conception to explain motor epileptiform seizures [12]. "In disease,

the range of paralysis and the sequence of spasm will represent sums of fixed orders of co-ordinations. To take a case in which the convulsions are limited to one side: the spasm affects the forearm, then the upper arm, the face, the thigh, and lastly the foot. Such sequences will represent the sums of the fixed time-relations these regions bear to one another in the part of the nervous system discharged.

"When records of such cases in which the spasm extends to the second side are obtained, the presumption is that sequences will be disclosed which will show the time-relation of physiological regions of the limbs of the other side; for illustration's sake such relations as we see in quadrupedal walking."

These views put forward by Hughlings Jackson are also verified in the sphere of sensibility by the recent researches of Dusser de Barenne. Working with his strychnine method, he found that from certain parts of the cortex of one hemisphere sensory disturbances could be produced on both sides of the body, as paræsthesiæ on one fore-limb and on the hind-limb of the opposite side. He calls this "crossed symptoms."

The first clinical analogy to Dusser de Barenne's experimental observations was described by Pötzl [23]. He diagnosed an abscess of the right frontal lobe, which was found on operation. The patient gave a history of sensory Jacksonian fits beginning simultaneously in her right hand and forearm, which sometimes spread to the left arm. At other times the paræsthesiæ passed from the left arm to the right leg. Pötzl explains this striking symptom by assuming an automatic mechanism for walking, in which the left arm and the right leg move simultaneously forwards and backwards.

Pötzl [24], who was then unaware of Dusser de Barenne's paper, recorded this case later in another paper, in which he quoted Dusser de Barenne.

Goldstein, in a paper already referred to, found that the face, thumb and big toe stand in a special relation to one another, and Popper's observation shows that the tips of the fingers may also have particularly fixed co-ordinations.

From these facts the conclusion is justified that the shape of the body may also have such a fixed co-ordination in time. The march of the paræsthesiæ in sensory Jacksonian fits therefore frequently follows the direct order of the parts of the body. But I must again insist that we cannot assume that all these functions are localized on certain fixed or preformed parts of the cortex.

There is also the interesting fact that these paræsthesiæ have often

a pre-axial or post-axial arrangement, similar to the distribution often found in sensory defects. The existence of a functional pattern may explain this too. We know that the pre- and post-axial representations depend on ontogenetic development, which is in its first stages determined by metameric arrangements. Possibly this distribution of the paræsthesiæ may depend also on special functional patterns, relics of an earlier stage of development. This conclusion is, I believe, supported strongly by one of my observations, in which a sensory fit (Case 5) spread from the shoulder down the ulnar aspect of the arm to the ulnar fingers, and ascended then on the radial aspect of the arm. There was a similar march in the leg. Here the paræsthesiæ spread in the order of metameric innervation, and from this fact we may infer that there must be in the brain a representation of the metameric or axial arrangement.

Russel and Horsley [25] have concluded from their case that there is a special localization of the pre- and post-axial halves of the limbs. Head [10] criticizes this view, writing: "No better example could be given of the difference between the older methods of thought and the conceptions I have attempted to put forward in this paper. Sensation is a psychical act, and even the regional representation of the processes on which it depends is based on functional habits, rather than on phylogenetic development. Each digit is a unit and can be used in an isolated act, either of motion or sensation; as such it is represented topographically on the cortex."

It is true, as Head has pointed out, that the case of Russel and Horsley is not conclusive. But my own cases, in which the paræsthesiæ spread in a manner which can only be explained by a metameric arrangement, seem to show that there may be in the brain also a metameric representation. This arrangement does not replace the representation of "functional habits," but exists, I assume, side by side with it. During that period of individual development when a metameric plan only exists, the brain is already developed to a certain degree, and it may be assumed that in it there is a metameric representation and that relics of this may remain in the fully developed brain. It is not necessary to assume a preformed or fixed localization, but only an old functional mechanism or pattern, analogous to Head's "schema." That these are only relics which later disappear seems probable from the relatively infrequent occurrence of fits of this type.

Another important fact obtained from my clinical observations is that in one and the same case there may be different marches of the

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paræsthesiæ. This is quite plainly shown by case L. R. and by Popper's case. In the former the fits commenced sometimes with a visual warning followed by paræsthesiæ in the big toe, which spread up his leg to his arm. Sometimes, however, the sensations began in the fifth, fourth and third fingers and then appeared in the upper lip. In Popper's case attacks limited to the tips of the fingers occurred, but the patient also described sensory seizures starting in her left arm, going down her body and then up to her head.

If we may assume that the same part is discharged always in the same patient, this fact would suggest that one point of the cortex may give rise at different times to different reactions. This, indeed, agrees with experimental observations. I refer to the researches of Leyton and Sherrington [15] on anthropoids, in which they found that the same point of the electrically excitable cortex gives different reactions according to different sequences of stimulation, i.e., whether the stimulus is moved from above downwards or inversely. Head [11] has emphasized this important fact. In his recent paper on aphasia he writes in the introduction: "These luminous experiments show the fallacy of conceiving the motor cortex as the seat of strictly limited 'centres' of pre-ordained function. Cortical activity, even when aroused by electrical stimulation, is revealed as a march of events with a definite temporal relation. The response obtained from any one point, at a particular moment, depends on what has happened before. Excitation of a spot which caused flexion of the elbow, may provoke the opposite effect if it follows some event, motor or sensory, favourable to extension. In the same way an area, associated at one time with contraction of the face, may yield movements of the elbow if approached from above downwards on the precentral gyrus. The past plays a predominant effect in the response obtained at any one moment, and this in turn helps to determine in advance the form of the future reaction."

There are, I believe, other biological considerations, especially emphasized by v. Uexküll [29], which also suggest that the brain, like all living tissue, is not a fixed system of pre-ordained centres and pathways, but is capable of adaptation in a high degree. V. Uexküll writes in his chapter, "The Problem of Protoplasm," that protoplasm has, in addition to its mechanical properties, explainable by physics and chemistry, other "super-mechanical" (übermaschinelle) properties. As such he means adaptation, regeneration and propagation. These properties are possessed by undifferentiated protoplasm only; the structures derived from undifferentiated protoplasm lose these "super-

mechanical" properties in proportion to the degree that they attain mechanical properties. Clinical and physiological experiences indicate that there may be in the arrangements of the structures themselves mechanisms for adaptation. Head [10] says, for instance, "Adaptation, biphasic activity and facilitation form a normal part of the vital activity of the nervous system."

It was Hughlings Jackson [13] who first conceived this idea with the intuition of a genins. He distinguished more highly and less highly organized activities in the nervous system. By more highly organized activities he meant those which function automatically, in which there occurs always the same response to a certain stimulus, so that the responses can be predicted with certainty. Such are, for instance, the vital and visceral reflexes, as the circulation of blood and respiration. They are represented in the lowest level of the nervous system, and they remain unaffected the longest in dissolution of the nervous system. The highest and most elaborate activities, which are represented in the highest level, are regarded by Jackson as the least organized ones. This means their responses are not so certain and uniform as those of the more organized activities, and they are consequently able to adapt themselves to numerous and complicated conditions. These higher reactions cannot be predicted; as Head [10] writes: "Therefore, between the impact of some physical force on the tissues of the body and the psychical act of sensation are interposed reactions which, in many cases, cannot be predicted."

This view is supported by the results of recent researches. On the one hand, by the investigations of Leyton and Sherrington [15], and on the other are the researches of Pötzl and of Fuchs on cerebral visual disturbances produced by wounds of the skull. Pötzl [21] in 1917, in the introduction to his paper on experimentally induced dream-images in their relations to indirect vision (p. 280), wrote: "Experiences from bullet wounds of the skull seem to show that the activities of the central parts of the visual fields can sink to the functional level of the peripheral parts of the field, and that peripheral parts can rise to a functional level more or less equal to that of the central parts of the fields."

Further, Pötzl writes in his paper on the treatment of lesions of the skull (p. 337): "Peripheral vision performs in these cases more than peripheral vision in healthy people; this seemingly paradoxical fact shows that some compensatory process has occurred, and that we are here in the presence of cerebral processes in some way analogous

to that which occurs in the development of a parafovea in squinting patients."

Fuchs [5] found that in some cases of hemianopia the remaining visual field is not simply half of the previous normal field, but that a new though smaller visual field, analogous to the old organized field, has developed. A new macula, that is another new point of most distinct vision, is developed which has analogous relations, as regards its position in the visual field, to the old macula in the normal field.

In attempting to explain the different marches of sensory Jacksonian fits, we may assume that first of all they may be determined by the intensity of the stimulus. If the excitation is slight, only a quite limited part of the body is affected, as the thumb and index finger, while if it is stronger the excitation extends, and may follow a preformed functional pattern in the "schema" or some other functional mechanism. In this case only the aura or initial symptom has any value in the localization of the excitation. This conception corresponds to Jackson's older views on epileptiform seizures, and also to the present-day physiological conceptions of the nature of the functions of the nervous system.

It must, however, be borne in mind that the forms which the fits take depend also on the actual disposition of the nervous system and on preceding stimuli, as has been shown by the experiments of Leyton and Sherrington.

C. and O. Vogt [31] have also found that the epileptic seizures provoked by experimental stimulation of the cortex differ according to the point to which the stimulus is applied. They write: "Our assumption that the dissimilar functions of certain areas of the cortex are manifested by particularities in the epileptic seizure is confirmed."

Conclusions.

(1) Sensory Jacksonian fits may be grouped into different classes, according to the manner in which the paræsthesiæ spread.

(2) The first class contains cases in which the sequence of the parts of the body affected by paræsthesiæ corresponds strictly to the arrangement of the sensory points in the post-central gyrus. Especially characteristic in this class is the spread of the paræsthesiæ from the thumb to the corner of the mouth. The paræsthesiæ tend to remain limited, or extend only slightly.

(3) The second class consists of cases in which the paræsthesiæ spread over the whole half of the body. Here the sequence does not

correspond strictly to the order of the cortical points. Especially characteristic of this class are the sequences, face, neck, shoulder, arm, fingers; or toes, leg, finger, arm, face. These sequences may correspond to a "schema" of the body.

(4) Finally, the march of the paræsthesiæ may correspond to an axial type, such as is well known to occur in defects of sensibility (pre- and post-axial type). The paræsthesiæ spread either along the radial or ulnar aspect of the arm, or along the anterior or posterior side of the leg. Sometimes they descend on the one side and ascend on the other.

(5) Other cases are described in which sensory fits followed other functional patterns (the tips of the fingers).

(6) The most satisfactory explanation of these phenomena is in accordance with the views of Hughlings Jackson, Sherrington and Head. If the stimulus is weak the paræsthesiæ do not spread widely, and then they correspond with the order of the sensory points in the post-central gyrus. If the excitation extends it follows certain functional patterns, which must not be regarded as pre-ordained centres and pathways. Such functional patterns are, for instance, the tips of the fingers (Popper), the corner of the mouth, the thumb and the big toe (Goldstein), Head's "schema" of the body, and finally, the pre- and post-axial types. The latter may depend on ontogenetic factors.

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PHYSIOLOGICAL STUDIES ON THE PATELLAR REFLEX.

I.—The Patellometer.

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For many years the knee-jerk has been the subject of wide investigation, both in normal and pathological individuals. From a physiological standpoint, however, its nature is imperfectly understood, and is a topic of much discussion. The most acceptable view, at present, is that this phenomenon is a true reflex. Two main pieces of evidence have been put forward against such an interpretation: the first is that the contraction curve of the quadriceps muscle in the knee-jerk resembles a simple twitch which is in opposition to the well-established fact that all reflex contractions are of a tetanic nature, and the second is that the latent period of the knee-jerk is shorter than that of most other reflexes. Sherrington [1] has already shown the invalidity of the first argument by showing that the extensor thrust, which is unquestionably a true reflex, is as brief as the knee-jerk, and concludes that "the mere brevity of the period of contraction of the knee-jerk is therefore no good evidence that it is not reflex." On the other hand, Jolly [2], who has done a careful investigation on the time relations of the knee-jerk and other reflexes, by means of the string galvanometer, also concludes that the knee-jerk has a reflex origin. Studies on the patellar reflex, however, have dealt almost exclusively with its latent period and the form of the muscular contraction. In observing the latency of response, by recording the moment of stimulation and the movement of the leg, the inertia of the leg was not always taken into consideration. Dodge [3] has shown that the leg's movement takes place much later than the contraction of the quadriceps muscle. The direct record of the muscle contraction, however, does not solve the problem, for the majority of the instruments used also have a considerable inertia. The use of the string galvanometer to record the electrical variation of the muscle involved in the knee-jerk would seem a reliable method, for the inertia of this instrument is so small that it becomes negligible. Jolly [2] reports, however, that the latent period, as measured with the string galvanometer, varies from time to time, and that the form of the

electrical variation is not always the same. Based on data obtained by means of different methods, the authors have reported inconsistent results, due in all probability to the different methods employed in eliciting the knee-jerk. Sherrington [1], François Frank [4], and others, observed that the latent period of a reflex act varies with the intensity of the stimulus—the stronger the stimulus, the shorter the latent period. It appears, therefore, that unless the intensity of the stimulus is maintained constant, the latent period does not afford a

FIG. 1.

reliable means of judging the reflex excitability of the nervous centres. On the other hand, the initial tension of the extensor muscle must be taken into account, for Pachon and Petiteau [5] have observed that the threshold of excitation in the knee-jerk is in part dependent on this factor.

The form of the muscular contraction is another point which has not received quite satisfactory solution; single twitches, double contractions with clonic and tonic phases and curves with oscillatory shapes have been found in normal subjects and described as normal types of the muscular contraction. It seems evident, therefore, that the

latent period and the form of the muscular contraction are not reliable indications of the conditions of the nervous centres governing the knee-jerk. This situation appeared to the author to necessitate another series of investigations on the patellar reflex, taking into consideration the threshold of excitation, that is, the minimum intensity of stimulation necessary to produce the first perceptible response. For this purpose an instrument was designed by the author, which may be conveniently called a "patellometer," and with which the threshold of excitation can be accurately measured. This instrument, as can be seen in fig. 1, is based on the pendulum principle, that is, a hanging hammer falls from different heights and strikes the patellar tendon with different intensities. The patient sits on a chair, or lies on a bed, with the thigh on the horizontal bar of the stand and the leg hanging freely. The stand, of telescopic construction (a brass tube of 1 in. diameter), measures 14·5 in. in height when closed, and has an extension of 12 in., so that it can be raised or lowered at will. The operator, by adjusting the movable parts of the instrument, fixes the hammer in such a position that it gently touches the skin on the patellar tendon and coincides with 0° in the scale graduated on the semicircle. All the adjustable parts of the instrument are also graduated in centimetres, so that the reflex can be tested at any time under the same conditions, viz., initial tension of the quadriceps muscle, the part of the tendon on which the hammer strikes, and so forth. Straight lines engraved on the several segments of the instrument facilitate the maintenance of the angles always at 90°. Sliding on the edge of the semicircle, there is a mechanism to hold the hammer's handle at any desired level. This mechanism is attached to the spring of an electro-magnetic device, and it can be withdrawn and the hammer released by tapping a key interposed in the circuit supplied by batteries with a total E.M.F. of about 4 volts.

To determine the energy with which the hammer strikes the tendon, we may consider it as a freely falling body under the action of gravity, for the effect of friction is small and beyond the precision of our measurements, and as such it is entirely negligible. A body falling under the action of gravity alone possesses kinetic energy which is a function of the mass of the body and the square of its velocity, i.e., K.E. $= \frac{1}{2}$ m V^2, where :

m = mass, in grammes,
V = velocity, in centimetres per second.

The velocity is itself a function of the distance through which the

body falls and the intensity of the acceleration due to gravity, i.e., $V = \sqrt{2 g h}$, where :

V = velocity, in centimetres per second,
g = acceleration due to gravity, in centimetres per second,
h = height of fall, in centimetres.

But,

$$h = r - (r \cos \alpha) = r (1 - \cos \alpha),$$

where : r = radius of the circle described by the hammer,
α = angle made with the vertical.

Therefore,

$$V = \sqrt{2 g r (1 - \cos \alpha)}, \text{ and K.E.} = m g r (1 - \cos \alpha).$$

For instance, taking the following values :

m = 153 grammes = weight of the hammer,
g = 980 centimetres per second $^{-2}$,
r = 20 centimetres = distance from c.g. of hammer's head to *centre* of circle of which are described by hammer is a part.
α = 300.

That is,

$$\text{K.E.} = 153 \times 980 \times 20 (1 - \cos 30),$$
$$= 3{,}000{,}000 (\cdot 134),$$
$$= 402{,}000 \textit{ ergs}.$$

In order to avoid the use of large numbers, it is proposed to use in this connection a unit, the "patellerg," represented by ϕ, and which shall be equal to 100,000 ergs, that is,

$$\phi = 1 \text{ patellerg} = 100{,}000 \text{ ergs}.$$

Therefore, the above result, namely, 402,000 ergs, shall be represented as $4 \cdot 02\ \phi$.

The scale on the semicircle is graduated both in degrees and patellergs, so that the intensity of the stimulus can be read directly without the necessity of calculation.

The "patellometer" was shown at the meeting of the Physiological Society held at London (University College) on March 21, 1925. It is constructed by Messrs. Baird and Tatlock, Ltd. (London), to whom the author is indebted for allowing him the use of fig. 1, which is a copy of the picture published in their Supplement Catalogue for 1925.

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HÆMANGEIOMA OF THE PIA MATER CAUSING COMPRESSION PARAPLEGIA.

BY PERCY SARGENT, F.R.C.S.

Amongst the lesions which may give rise to symptoms closely resembling those of spinal tumour is one consisting of a more or less localized mass of blood-vessels, nævoid in character, lying between the pia and the arachnoid. In most cases these angeiomata are venous, but occasionally they are arterial.

The condition seems to have been first noted by Gaupp in 1887 (quoted by Cobb [1]). He quoted the case of a female, aged 45, with a history of weakness of the legs and paræsthesiæ commencing at the age of 21 and slowly advancing for ten years. During the next four years improvement occurred, so that she was able to get about. Then both legs suddenly became spastic and anæsthetic, with loss of sphincter control and vasomotor paralysis. The condition improved a little, but for ten years she remained a cripple and finally died of "decubitus infection." On post-mortem examination a large venous varix was found pressing upon and flattening the cord. The five following cases are also referred to by Cobb :—

Berenbruch, 1890. A male, aged 16, after severe exercise felt pain and weakness in the legs. At the end of two weeks the right leg was entirely paralysed and the left partly so, with increased tendon reflexes. There was a relative loss of sensation up to the umbilicus. Operation was performed two and half months after the onset, with a fatal result. On post-mortem examination a cavernous plexus of veins was found along the spinal column, connecting with a similar intraspinal mass through the intervertebral foramina. There was an angeioma compressing the cord from the fifth cervical to the third thoracic segments.

Gerhardt, 1895. A male, aged 18, complained of weakness of the right leg followed a week later by weakness of the left leg. Two months later there was total paralysis of the legs with loss of sphincter control, increased tendon-jerks and partial sensory loss up to the umbilicus. During the next two years the anæsthesia became complete. Death occurred from bedsores after six years, and at the autopsy a vascular mass was found compressing the cord at the fifth thoracic segmental level.

Harman and Balk, 1900. A man, whose symptoms commenced with pain in the legs lasting for four months before weakness developed. All the symptoms gradually passed off in about six months. Two years later he had a similar attack from which recovery occurred sufficiently to enable him to walk. A third attack occurred two years later, but it was only slight, and improvement was again taking place when he had a sudden attack of pain with retraction of the head and loss of sphincter control. Death occurred ten days later, and at the autopsy a cavernous angeioma of the pia was found overlying the lumbar cord, with a large blood-clot in the spinal canal.

Lorenz. A female, aged 26, complained of weakness in the left hand, and two days later there was sudden sensory and motor paralysis of the legs, with loss of power in the arms. She died three days later, and post mortem an angeioma the size of a cherry was found at the level of the seventh cervical segment, with hæmorrhage into the subarachnoid space and into the substance of the cord.

Hadlich, 1903. A female dwarf, aged 35, died after Cæsarean section. On post-mortem examination an angeioma of the pia was found in the lumbar region, invading the cord and causing marked distortion.

Raymond and Cestan, 1904 [6]. A youth of 17 complained of pains at the back of the neck, radiating into the right arm, and progressive weakness of the right limbs. The right arm showed an Erb type of paralysis, with wasting and reaction of degeneration in the muscles. There was diminution to all forms of sensibility in the parts supplied by the cervical segments of the cord. A diagnosis of "myelitis" was made, and mercurial treatment was carried out. The symptoms, however, progressed and the left arm became affected. Operation was decided upon but the patient died of broncho-pneumonia before it could be carried out. At the autopsy the cervical cord was found surrounded by a network of vessels, especially on the right side. The vessels penetrated the cord, and were tortuous, varicose and aneurysmal, some being as large as a quill. The mass commenced near the bulbo-pontine junction and disappeared progressively towards the second thoracic segment. There was sclerosis around the vessels which penetrated the cord. Arteries, veins and capillaries all shared in the dilatation.

Fedor Krause, 1906 [5]. Under the name of angeioma venosum racemosum, Krause described the lesion in the case of a man, aged 34, who had had symptoms of spinal tumour for seven years. A laminectomy was performed from the sixth to the twelfth thoracic vertebræ.

A mass of wide thin-walled tortuous vessels was found, some of which he ligatured. The patient died three months later, and at the autopsy only remnants of the spinal cord tissue were found at the site of operation.

Jumentié and Valensi, 1911 [4], recorded a case in a man, aged 40, who had suffered from flaccid paraplegia for three years. The autopsy revealed an extradural venous plexus surrounding the roots and posterior root ganglia. On opening the dura, a mass of turgid tortuous veins protruded, which resembled a varicocele (*intestin de poulet*). The mass was confined to the posterior aspect of the cord and extended from the sixth cervical to the seventh thoracic segments. The patient had been operated upon for varicocele fifteen years previously.

Stanley Cobb, 1915 [1], recorded the case of a boy, aged 8, whose clinical history is very remarkable. The first symptom was a sudden sharp pain in the back which passed off in four days. He returned to school apparently well, and three days later a similar attack of pain occurred in the back, only more intense, and at the same time the left foot felt numb. The numb feeling spread up the leg to the thigh and then down the other leg until, at the end of fourteen hours, both lower limbs were numb and paralysed. Next morning loss of sphincter control was noted. When examined there was complete flaccid paralysis with loss of reflexes, and anæsthesia up to the umbilicus. Two months later the tendon reflexes returned, together with a positive Babinski reflex. Laminectomy was performed from the sixth to the tenth thoracic vertebræ. On opening the dura a tangle of large vessels appeared overlying a flattened cord. No ligation was done, and the dura was left open. No relief followed. There was a large nævus of the skin over the right lower ribs behind, and three other smaller nævi at the same level.

Spiller and Frazier, 1923 [7]. A female, aged 25, had an attack of severe pain in the legs, which became weak and stiff, together with retention of urine which lasted for two weeks. She gradually recovered, and remained well for eight years, when the right leg began to get stiff and weak. Sensation was affected in the sacral root areas, and sphincter control was again disturbed. A laminectomy was performed of the twelfth thoracic and first lumbar vertebræ. The lesion, which was situated at the level of the first lumbar segment, consisted of convoluted varicose vessels of various dimensions, which seemed to extend well down along the right side of the cord and to a lesser extent down the left side. The largest of the vessels was ligated. The patient became

worse for a time, but gradually improved until she reached the same state as before operation.

Elsberg, in 1916 [2], placed it on record that in 120 laminectomies for spinal disease he had found much enlarged veins on the posterior surface of the cord in six cases; all of these had symptoms of a level lesion, and the greatest enlargement of the veins was found at the level indicated. Two of the patients had spastic paraplegia, with sensory loss, of long duration, and were not improved by operation. Two others had symptoms similar to those of spinal tumour; in one case considerable improvement followed operation, whilst the other patient recovered completely in three months.

In all the cases cited above, except that of Raymond and Cestan, the vascular mass has consisted of dilated tortuous veins only, constituting a veritable venous angeioma, and four of the cases which I now report have been of the same nature.

Case 1.—H. H. S., male, aged 31. Patient of Dr. Kinnier Wilson. In October, 1919, whilst moving a ladder, he experienced a sharp pain in the back which felt stiff and painful afterwards. Three months later the pain had completely gone, but it returned soon afterwards whilst the patient was gardening, and remained. When admitted to hospital the legs were said to be painful in a varying manner, first one and then the other. On one occasion the left leg had been stiff for a few days. No objective neurological signs of disease were made out, but the cerebrospinal fluid was golden-yellow in colour and contained 0·6 per cent. of protein. The Wassermann reaction was negative. In March, 1921, an exploration of the cauda equina was decided upon, for which purpose the laminæ from the eleventh thoracic to the third lumbar vertebræ were removed. A small mass of convoluted dilated veins was found lying on the posterior aspect of the cord at the first lumbar segmental level. It was left untouched, and the theca was closed. The patient made an uninterrupted recovery, and left the hospital six weeks later. Four years later he reported that he was quite well and at work (fruit growing), but that he still had some pain in the back and down the front of the legs. "It is a tingling sort of pain and is worse when I have been either walking too much or doing too active work, or in bad weather."

Case 2.—E. P. H., male, aged 52. Patient of Dr. R. H. Jamieson. Symptoms began with pain in the left hip, thigh, calf, and outer side of foot, with tingling and weakness in the leg and a subjective "dead feeling" in the perineum. When examined there was no sensory loss anywhere, and the only weakness elicited was that of difficulty in standing on tiptoe with the left foot. The ankle-jerk was absent. The Wassermann reaction was strongly positive, and antisyphilitic treatment was given. Improvement took place, but six months later the symptoms recurred—a feeling of "pins and needles" being experienced, first in the left leg and then in the right. Some six months later,

again, the weakness recurred, together with slight difficulty in starting the act of micturition, and numbness round the anus. Three years later he was seen again when the lower limbs were found to be weak and spastic. Both plantar reflexes were extensor; the right tendon-jerks were absent and the left present; the abdominal reflexes were absent below the umbilicus. There was loss of sensibility to pin-prick below the umbilicus, together with loss of vibration sense and impaired postural sense up to the same level. In December, 1923, a laminectomy was performed and a mass of enlarged, tortuous varicose veins was found, evidently arising in the pia mater, spread over an extensive area of the posterior aspect of the mid-dorsal cord. Nothing was done to the veins, but a decompressive effect was obtained by leaving the theca unsutured. After operation a bedsore developed, together with cystitis, both of which took a long while to clear up. When seen fifteen months later the power in the legs had improved proximally, but the ankle movements were feeble. He was able to get about wearing a toe-elevating mechanism. The bladder was normal, but the sensory loss was very much as it had been before the operation.

Case 3.—H. J. S., male, aged 38. Patient of Dr. H. M. Rainsford and Dr. J. L. Birley. In 1917, following a fall from a horse, he had violent "pins and needles" down the right leg. This lasted for several weeks and complete recovery took place. In 1922, he experienced difficulty in starting the act of micturition, and three months later pain was felt at the level of the right ninth thoracic root, together with increase of the bladder symptoms. The pain persisted, and nine months later the right leg became weak, for a few hours only. Shortly afterwards he experienced pain down the back of both legs, more in the right than in the left, and this was followed by progressive difficulty in walking and increased bladder trouble, together with partial loss of rectal control. The Wassermann reaction was negative, but eighteen injections of mercury were given and marked improvement followed. Six months later the cerebrospinal fluid showed thirty small lymphocytes per cubic millimetre, and a slight increase of globulin. The Wassermann reaction was again found to be negative. At this time there was found to be weakness and slight wasting of the legs and thighs, more on the right side. The right knee-jerk and both ankle-jerks were absent and the plantar reflexes uncertain. The abdominal reflexes were also uncertain. Sensibility to pin-prick was grossly defective over all the sacral segments. Vibration sense was much diminished in the right foot, and there was considerable loss of postural sense in the right toes and ankle. Anti-syphilitic treatment was again carried out, and in four months the condition had improved greatly, especially as regards the sphincters. There was marked variation of symptoms from day to day and even from hour to hour. The plantar reflexes, however, were now definitely extensor in type. In December, 1923, there was a fresh increase in the bladder symptoms, with rectal incontinence. Postural sense was defective in the right foot, ankle and knee, and in the left foot and ankle, whilst vibration sense was deficient up to the tenth thoracic segmental level. Lipiodol radiograms showed a partial obstruction.

In March, 1924, a laminectomy was performed from the seventh to the tenth thoracic vertebræ. A diffuse hæmangeioma was found lying on the posterior aspect of the cord from the tenth thoracic segmental level downwards for three or four segments. The theca was left unsutured. Some improvement took place afterwards, but the symptoms continued to vary from time to time, and on the whole it was doubtful whether much benefit had resulted from the operation.

Case 4.—Male, aged 53. Patient of Dr. Gordon Holmes. Two years before the onset of symptoms he was knocked down by a falling branch of a tree. He fell with right leg doubled under him; was able to get about in three weeks. In March, 1924, there was a sudden onset of excruciating pain in the legs, which persisted for a week. He recovered and remained well until October, 1924, when the pain recurred and persisted, but varied in severity. Pain was felt in outer side of legs, front of thighs and feet. This was followed by a cold numb feeling in same area, worse on the right than the left side. There was some difficulty with micturition, and slight loss of rectal control. Some wasting and weakness of right lower limb were noted, especially with extension of the knee and dorsiflexion of the foot. The abdominal reflexes were present, except in the lowest segments. The ankle-jerks were absent, and the plantar reflexes flexor. Sensibility to pin prick and cotton wool was diminished up to the twelfth segmental level. The gait was feeble and uncertain. After this considerable improvement took place, and in December, 1924, he was able to walk a quarter of a mile without a stick. A few days later he began to have falls and needed two sticks for walking, but this was again followed by improvement. In February, 1925, the thighs were wasted and flabby, and all movements of the lower limbs were weak, especially on the right side. The plantar reflexes were extensor, the knee-jerks and angle-jerks were absent, and the abdominal reflexes were absent up to the eighth thoracic segmental level. Sensibility to pin prick and light touch and vibration sense were diminished to the same level. The cerebrospinal fluid was slightly yellow and contained 0·1 per cent. of protein with five cells per cubic millimetre. Lipiodol radiograms showed no block. A fortnight later the legs were weaker, and the sensory loss had reached up to the tip of the xiphoid.

A laminectomy was performed, the arches of the lower six thoracic vertebræ being removed. On opening the theca a mass of dilated tortuous veins was seen extending over the dorsal surface of the whole area exposed, whilst at the level of the seventh segment there had evidently been some thrombosis in the mass of veins. Four of the largest vessels were ligatured. After the operation the patient had retention of urine for some weeks, and for a time a slight increase of lossof power in the lower limbs. In the middle of March, however, he began to move his legs, particularly the right, more strongly than he could before the operation. The recovery of power was slow and progressive for about six weeks. He was then able to stand without assistance; he could not walk alone owing to difficulty in maintaining his balance.

Sensory loss remained unchanged for about two months; after this time he began to regain cutaneous sensibility, especially on the right side of the abdomen and the right leg. The sense of position and the appreciation of vibration also improved slightly. About two months after the operation he also regained further control over his bladder and was able to empty it without external help. During the first half of May his condition remained stationary, but in the latter part of this month his power of walking improved. His knee-jerks and ankle-jerks still remain absent, the left plantar response is definitely extensor, but the right is sometimes flexor and sometimes indefinite. The sensory disturbance has, however, remained much as it was. He has since reported that during an attack of cystitis in June the power of his legs deteriorated, but he has regained it. He can now only walk with assistance, or he can get round a billiard table holding on to it. Apparently there has been no recovery since he left London five weeks ago.

The pathology of these venous angeiomata is by no means clear, but they resemble the congenital nævi found elsewhere in the body, and may perhaps be regarded as of the same nature. The occurrence of similar skin nævi at the same segmental level in Cobb's case lends support to this view. The symptoms occur at all ages, the youngest patient having been 8 years old, and the oldest 53. Of fifteen patients, eleven were males and four females. With regard to the segmental level, in fourteen cases in which this is specified, three were cervical, six mid-dorsal, and five lumbar. There is nothing noteworthy therefore either as regards age, sex, or segmental level, which might assist in differential diagnosis.

The clinical history, however, may be of great diagnostic value. In some cases the onset has been acute, with rapid development of paralysis, leading to a diagnosis of "myelitis," and in two cases a fatal termination was apparently due to intrathecal hæmorrhage. But the most striking feature in several of the cases in which a detailed history is available was the remarkable manner in which the symptoms varied from time to time. In one of my cases the symptoms varied from day to day and sometimes even from hour to hour. The length of history during which "attacks" occur from which more or less complete recovery may take place is another striking feature. Thus in the case of Spiller and Frazier there was a period of eight years between two "attacks," during which the patient was quite well. In Gaupp's case the history was spread over twenty-four years, during which time there was a period of four years in which the patient was considerably improved. In one of my cases symptoms had been present for four years, and during this time there had been several periods of marked improvement.

The cerebrospinal fluid was examined in three of my cases. In one it was of a golden-yellow colour and contained 0·6 per cent. of protein; in another there was a slight increase of globulin, with thirty small lymphocytes per cubic millimetre; and in the third it was of a pale yellow colour and contained 0·1 per cent. of protein with five cells per cubic millimetre.

The characteristic variability of the symptoms makes it difficult to estimate the value of operative interference, and it is at least doubtful whether any real benefit was derived from operation in any of my cases. In so far as the symptoms may be due to compression, which may be assumed to vary from time to time with congestion or œdema, the decompressive effect secured by opening the theca and leaving it unsutured may be beneficial; but it is clear that the symptoms are not wholly produced by mechanical pressure, and that they are more probably due to circulatory disturbances in the cord. Whether any attempt ought to be made to remove or cause thrombosis in the veins of the angeioma I am not prepared to say, but the risks of serious injury to the circulation in the cord would seem to forbid any such procedure. The mere ligation of several of the veins, which I have practised, seems to be harmless but ineffective.

Arterial Angeioma.

The following case of arterial angeioma (aneurysmal varix; plexiform angeioma; cirsoid aneurysm) involving the pial vessels is of interest in connection with the foregoing cases:—

A naval stoker, aged 44, had suffered for two years with increasing weakness of the right arm, wasting of the hand muscles and pain in the shoulder. Soon after the onset he began to lose powe and postural sense in the legs, and this was followed by incontinence of urine. On examination there was no voluntary power in the legs, but reflex flexor spasms could be obtained in them on stimulation. There was profound sensory loss up to and including the first thoracic segment. There was retention of urine. The knee-jerks were absent, the ankle-jerks present, the plantar reflexes extensor, and the left abdominal reflex absent. The cerebrospinal fluid contained 0·17 per cent. of protein. The Wassermann reaction was negative. It was noted that a very large tortuous artery crossed the left supra-clavicular fossa, presumably the transversalis colli. An exploratory laminectomy was commenced but had to be abandoned on account of hæmorrhage. The muscles and bones were permeated by numerous dilated, tortuous, thin-walled arteries, some of which were as large as the radial artery. The condition was evidently one of diffuse aneurysmal varix. Death occurred shortly after the operation. At the autopsy a condition was found inside the spinal canal similar to that obtaining in the muscles and bones. The cord was

found to be compressed at about the seventh cervical segmental level by an aneurysm containing recent clot (fig. 1). A transverse section at the level of the aneurysm, made by Dr. J. G. Greenfield, showed that the vessels within the cord were not affected.

FIG. 1.

Elsberg [3] mentions a case in which the cervical cord was compressed by an aneurysm, but this was apparently unconnected with any arterial angeioma like that in the case quoted. The only other recorded case which may have been similar in nature is that of Raymond and Cestan, where it is noted that the arteries as well as the veins and capillaries shared in the dilatation.

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Proceedings of the Section of Neurology of the Royal Society of Medicine.

Meeting held on February 12, 1925.

Dr. A. F. Hurst read a paper on "The Ætiology and Treatment of Subacute Combined Degeneration of the Spinal Cord" (see p. 218).

DISCUSSION.

Dr. H. J. Macbride said that in collaboration with Dr. Carmichael he had collected records of 199 cases of Subacute Combined Degeneration of the Spinal Cord from in-patients of the National Hospital, Queen Square, during the past twenty-five years.

Age, sex, heredity, distribution, seasonal incidence and occupation, as exciting or predisposing causes, were fully investigated in their series.

The first symptom complained of was of a neurological nature in 78 per cent. of the patients, while only the remaining 22 per cent. first complained of symptoms which could be classed as anæmic, thus showing that anæmia was not a causal factor of the disease.

They strongly emphasized the fact that in 55 per cent. of the females and 74 per cent. of the males no history of gastric disturbance previous to the onset of symptoms was obtained. Sore tongues, occurring either before or after the disease became apparent, were only found in fifteen per cent. of the cases.

Of the fifty-five cases investigated during the last three years, fourteen cases had free HCl in the gastric contents, on fractional test-meal examination; in four of these the diagnosis was confirmed by post-mortem examination.

In the light of these facts they could not support the gastro-intestinal intoxication theory, nor could they accept the fact that the absence of free HCl was a constant predisposing factor.

Turning their attention in other directions for a predisposing cause of this disease, they found that 96 per cent. of the females cease to menstruate one or two years before the onset of symptoms. This with the fact that many of the cases had a myxœdematous appearance and ran a subnormal temperature even up to within a few hours of death, led them to think of an endocrine disturbance as a possible predisposing factor. Seventeen cases were given thyroid, for which they were found to have a remarkable tolerance, all of them being able to take up to 30 gr. a day for weeks, without manifesting

any signs of thyroid intoxication. One possible explanation of this was that in this disease the tabloids of thyroid were not broken up in the alimentary canals, but in some cases a careful search of the fæces failed to discover any intact tabloids or portions of them. In one or two cases even the administration of the elixir of thyroid produced no symptoms.

They summarized their investigations as follows:—

(1) It is a disease of middle life, attacking equally males and females of all social grades and professions.

(2) There is no biannual curve of incidence.

(3) The evidence in favour of a gastro-intestinal infection as a predisposing cause is scanty.

(4) There is a certain amount of evidence to suggest the possibility of a disturbance of endocrine metabolism as being an essential factor in the ætiology.

(5) In the majority of cases neurological symptoms precede those of anæmia.

As treatment they had tried the following:—

For anæmia, arsenic by the mouth and injections of novarsenobillon; for oral sepsis, mouth washes and removal of bad teeth.

For gastro-intestinal intoxication, naphthalein tetrachloride and laxatives to prevent constipation.

For achlorhydria, dilute HCl in large doses after meals.

For endocrine deficiency, thyroid.

For avitaminosis, vitmar and roboleine.

For cholesterol metabolic disturbances, inunctions of lanolin.

Novarsenobillon in a few cases produced some improvement. Thyroid caused only a fleeting improvement in most of the cases to whom it was administered.

Blood counts were made after the various forms of treatment, and no increase in the number of red cells was found; this was in marked contrast to the remissions of pernicious anæmia.

Dr. WILLIAM HUNTER dealt at length with the ætiology of pernicious anæmia. He pointed out the frequency of peripheral paræsthesiæ in all cases. In eighteen out of his 200 cases of pernicious anæmia more definite symptoms of spinal disease were present. He had seen symptoms of combined degeneration develop in all stages of anæmia up to five years after its first symptoms commenced, or even during long remissions, or after permanent recovery from the anæmia. He also referred to one patient who was almost completely paralysed but had recovered.

Dr. F. A. KNOTT discussed the bacteriology of the duodenal infection, pointing out that frequently strains of hæmolytic streptococci could be obtained from here in case of pernicious anæmia.

Dr. JAMES COLLIER admitted that in many cases of combined degeneration the blood picture had been that of some stage of pernicious anæmia. He also described a case of chronic lymphatic leukæmia in which the

characteristic clinical and pathological features of combined degeneration were present. On the other hand he had never seen a case of pernicious anæmia which later developed subacute combined degeneration. He could not agree with Dr. Hunter's teaching that peripheral subjective sensations in the limbs were indications of organic changes in the nervous system, but was certain that tingling, numbness and other paræsthesiæ frequently occurred in all varieties of anæmia. He regarded it as dangerous to speak of a cure in in this disease, for though in rare cases great improvement may occur the patients invariably succumb.

Dr. STANLEY BARNES said that of the last twelve cases under his care only three conformed to the conditions which had been found in Dr. Hurst's cases. Of the other cases, in six there had been a subnormal acidity and some degree of anæmia, whilst in two cases the acid was normal, and in one a hyperacidity of the duodenal type was present. He also emphasized the difficulty in diagnosing early cases and the necessity to exclude with certainty cerebro-spinal syphilis, disseminated sclerosis and other nervous diseases that might produce similar symptoms. On the whole he believed achylia might be an important factor in the disease. If it is proved that combined degeneration is due to a gastro-intestinal affection, he suggested that the toxins might reach the spinal cord through the perineural lymphatics.

Dr. ELLIS stated that in his opinion Dr. Hurst's views must be held as non-proven, especially as to the pathogenicity of the streptococci. He related the details of a case of great interest, in which a man who underwent a partial gastrectomy for a growth of the stomach in 1909 (proved to be carcinoma on section) now presented the signs of subacute combined degeneration of the cord, with a sore tongue, achlorhydria and a blood-picture suggestive of pernicious anæmia.

Dr. HURST, in reply, said that despite criticism he must maintain that pernicious anæmia and subacute combined degeneration of the cord are different manifestations of the one disease. He was particularly interested in Dr. Collier's case of lymphatic leukæmia, in which combined degeneration developed. He suggested it might be merely a coincidence, but it was interesting that in one of the two cases of leukæmia which he had examined there was no free acid in the stomach.

Notices of Recent Publications.

Neurological Fragments. By J. Hughlings Jackson. With a Biographical Memoir by Dr. James Taylor. London: Oxford Medical Publications. 1925. Pp. 227.

There is always a danger that the names of great men become mere legends attached to one event or to a contribution to knowledge in which they played a part; by this alone they may be known, though it is frequently the least important and valuable part of their work. This is particularly true in the case of Hughlings Jackson; usually his name is only associated with the motor manifestations of local cerebral excitation. This was undoubtedly at the time it was made an observation of great importance, but in itself it was probably the least valuable of Jackson's contributions to neurology and to the physiology of the brain; Jacksonian fits would have been certainly described by another within the succeeding few years.

The real and essential importance of Jackson's discovery of local motor epilepsy lies in the fact that it led him to a series of reasonings which first threw light on the nature and function of the motor apparatus of the brain.

It was so with every subject in which he interested himself; symptoms were not for him mere signposts which lead almost automatically to the diagnosis of a nervous disorder, or permit its classification; he regarded every symptom as a manifestation of a disturbance of function which could, therefore, if rightly comprehended, throw light on normal function.

What neurology therefore owes to Jackson was a new method by which he deduced the normal workings of the nervous system from the mode of its reaction to disease.

There is, however, an almost sufficient excuse for the general ignorance of much of Jackson's work, as a large part of it is scattered through the pages of little known or now extinct journals; it is, in fact, not easy to search out any article even if its existence is known; consequently a large part of his publications is available only to English readers with access to good libraries.

Among the less known of his papers are a series of articles contributed to the *Lancet*, between the years of 1893 and 1909, under the title "Neurological Fragments." These are largely disconnected notes on any subject that at the moment of their writing claimed his attention. Some may be no longer of interest or importance, but in a large proportion some idea, suggested often by the observation of an apparently trivial symptom or by a paper he had read, is developed in Jackson's characteristic manner and made to throw light on the nature of normal function or of disease.

It is this series of articles which are collected in this book under their original title by Dr. James Taylor, who was one of Hughlings Jackson's pupils and most intimate friends. Dr. Taylor also introduces the volume by a short but excellent biographical memoir, which will be welcomed particularly by those who knew Jackson, but will be appreciated by all interested in the history of neurology. There are also included "Recollections of a Life-long Friendship," written by Sir Jonathan Hutchinson at the time of Hughlings Jackson's death, and a memoir by Dr. Charles Mercier, another of his pupils, which appeared on the same occasion.

The volume concludes with a complete list of Hughlings Jackson's published writings which will be of the greatest service to anyone who desires to consult his work. There is also an index of contents which will enable anyone in possession of the volume to read Jackson's views on the numerous subjects dealt with in these "Fragments."

The Cerebro-spinal Fluid in Clinical Diagnosis. By J. GODWIN GREENFIELD and E. ARNOLD CARMICHAEL. London: Macmillan and Co. Pp. 272. 1925. Price 12s.

The great advances that have recently been made in the pathology of the cerebro-spinal fluid and the application of the results obtained to clinical practice, have created demands for reliable textbooks by which pathologists can control their researches, and neurologists can learn the significance of the various deviations from the normal that occur in the fluid in disease. Several such monographs have appeared during the last fifteen years, but some, as Mestrezat's, are now out of print, and others are already out of date.

A new volume, especially written from the point of view of clinical diagnosis, must be therefore welcome to neurologists, and particularly one that is based on extensive personal pathological experience carefully correlated with clinical practice.

This book, by the Pathologist and the Resident Medical Officer of the National Hospital, will certainly fulfil these conditions. Although the authors, as their large bibliography shows, have collected all that is definitely known of the nature of the fluid and its variations in disease, the book is obviously, except as they admit in their preface in the case of some rare tropical diseases, based on their own experiences.

The first section is devoted to the nature and composition of the fluid and the pathological alterations that it undergoes; the second section deals with its characters in various diseases, while the technique of its examination is described in the last section where it can be easily consulted and yet does not disturb the clinician merely interested in end-results who consults its pages.

The book seems remarkably complete; even the most recent and the least well known "reactions" are fully described, and their value and significance are fairly and fully considered. It seems doubtful if it will fail to yield any knowledge available at present to those who consult its pages. At the same time it is concise and written in a pleasant and readable style.

Bibliographic references to the separate chapters are arranged at the end of the book, and a very complete and accurate index is provided which facilitates inquiries into its pages.

Lehrbuch der Nervenkrankheiten. Herausgegeben von H. CURSCHMANN und F. KRAMER. 2te Auflage, S. 952. Berlin: J. Springer. Price 36 M.

The first edition of this textbook, which is written by several well-known German neurologists, appeared in 1909. The present edition is of considerably larger compass, as many of the chapters are much extended in the light of further advances in knowledge; new contributors have been also introduced.

The book is essentially practical, but the completeness with which the subject-matter is treated distinguishes it from many other textbooks. Further, each subject is adequately illustrated by excellently reproduced figures, and the absence of an unnecessary number of references makes the reading of it easy.

The sections which particularly attract attention are those on the extrapyramidal syndromes, on diseases of the vegetative nervous system, on local symptomatology, and the special chapters on orthopædic treatment and on the surgery of the nervous system. The last of these by Krause is perhaps unduly long for a textbook of this size, but it serves to show general physicians how much surgical treatment can do, and to illustrate its difficulties and limitations.

The volume can be highly recommended as one of the most reliable textbooks of moderate size.

Les Nerfs en Schémas. Anatomie et Physiopathologie. Par A. PITRES et L. TESTUT. Pp. 706. Paris: G. Doin. 1925. Price 150 fr.

During the late war the authors of this volume were engaged in giving instruction on the elements of neurology to students and recently mobilized doctors. As a short time only was available for each course they employed simple anatomical diagrams and short notes on the nervous physiology in conjunction with clinical demonstrations. Convinced of the value of this method of teaching they decided to publish their charts and notes, but have succeeded in doing so only now

In the first 500 pages they deal with the anatomy and physiology of the cranial and spinal nerves, including the sympathetic, and the symptoms produced by injury or disease of them. The coloured plates and numerous figures by which this part of the book is illustrated give it a considerable value, but the clinical sections are not so satisfactory. The chapters on the central nervous system call for much adverse criticism. The anatomical diagrams are crude and frequently incorrect; for instance, the majority of the ascending sensory fibres are shown passing from the spinal cord and brain-stem directly to the cerebral cortex; in another, most of the fibres of the superior cerebellar peduncle are represented (and in the text described) as taking origin from the

cerebellar cortex, and in a third plate the accessory motor path consists of a descending cerebellar tract connecting the cortex of the cerebellum directly with the spinal cord. The authors are also frequently satisfied to present antiquated views in the sections on physiology.

Le Radio-diagnostic des Affections intra-rachidiennes par le Lipiodol sous-arachnoidien. By LOUIS LAPLANE. Paris: Amédée Legrand. 1924.

Dr. Laplane has, in this interesting and well-illustrated book, recorded a large number of valuable observations upon the use of Lipiodol-radiography in the diagnosis of intraspinal lesions, a method which was first described by Sicard and Forestier in 1922.

The dangers of this procedure are negligible, and in the majority of cases no ill effects of any kind follow. Pain, however, sometimes occurs, and may be of two kinds: (1) an accentuation of root pains already present, and due to the lesion, and (2) pain in the legs and tenderness over the coccyx lasting for several days. In a few cases there has been headache and sometimes there has been a transient rise of temperature of one or two degrees. The cerebro-spinal fluid was, in four cases, examined daily, and was found to show no changes, except a slight increase of polynuclear cells. The elimination of iodine by the kidneys lasts for many months. As regards the local effects, it has been noted that after a few days the lipiodol becomes, as shown radiographically, less mobile, and in some cases becomes fixed in the sacral cone. Opportunity of examining the tissues around the lipiodol was afforded by five post-mortem examinations made at intervals of from one to eleven months after the injection. In one case (three months) the lipiodol lay free amongst the lumbo-sacral roots, but in the rest it was found to be entirely fixed by an extremely thin layer of tissue. This tissue, however, when examined microscopically showed no trace of inflammation, nor were any macrophages found. In another case (eleven months) the lipiodol was encysted, and the macrophagic reaction associated with foreign bodies was found at the periphery of the cyst.

The technique of the method is described in detail, and sources of error are indicated. As regards the physical conditions, a high degree of viscosity of the fluid causes a tendency for it to stick to the walls by surface tension. Too high a percentage of iodine causes undue viscosity. Laplane advises that lumbar puncture should not be done within five or six days before the lipiodol injection, as cerebro-spinal fluid may continue to escape through the puncture into the epidural space, so diminishing the size of the sub-arachnoid space and retarding the flow of the lipiodol. Percussion of the spine immediately after the injection assists its descent. Cisternal injection is usually done with the patient lying on the side, and he is made to sit up immediately afterwards; in these circumstances the lipiodol takes about three minutes to descend to the bottom of the theca in a normal subject; it flows

rapidly as far as the fourth thoracic vertebra, then slowly, and afterwards rapidly again. The radiographic appearances of arrest by adherence differ from those in a true obstruction, partly because the former always occurs at about the fourth thoracic vertebra, and partly from the shape of the drops, which are said to resemble candle gutterings. The arrest of droplets which is sometimes seen is attributed to the lipiodol being impaled by calcareous plaques, or diverted into radicular culs-de-sac.

Laplane believes that although a negative result may be attained by both intramedullary or root tumours in their early stages, yet the presence of an intramedullary tumour may sometimes be indicated by the way in which the lipiodol descends, owing to approximation of the cord to the theca with consequent alteration in the conditions of surface tension. He also believes that root tumours can sometimes arrest the lipiodol before any pressure symptoms have appeared. He calls attention to the long time which may exist in cases of extramedullary tumour between the onset of the root pains and the pressure symptoms. This "pre-paraplegic stage" may last for from two to seventeen months. Such cases have been labelled "xanthochromic lumbago," being characterized by pain and rigidity together with yellow coloration of the cerebro-spinal fluid. The difficulty of distinguishing between such cases and Pott's disease is emphasized.

Helmholtz's Treatise on Physiological Optics. Translated from the Third German Edition. Edited by JAMES P. C. SOUTHALL, Professor of Physics in Columbia University. Published by the Optical Society of America. Vol. II: The Theory of the Sensations of Vision. Pp. viii + 480. 1924.

This volume forms a part of the first English Translation of Helmholtz's standard treatise. The third German edition was published in 1909-1911, and the editors responsible for it, Gullstrand, von Kries and Nagel, decided to ignore the second edition which had been left incomplete at Helmholtz's death in 1894, and to reprint the first edition, supplementing the original text with a number of notes written by themselves.

Some further new material has been specially prepared for the English translation, in order to bring the work up to date. In the volume now under review this takes the form of three notes by Professor von Kries on contrast, anomalous colour vision, and heterochromatic photometry, respectively, together with a chapter on the nature of the colour sensations by Dr. Christine Ladd-Franklin.

The first appearance of an English edition of this, the standard work on physiological optics, is an event which will be most heartily welcomed by British students of this science.

The form in which the book has been produced is in every way worthy of its subject-matter, and the translation leaves nothing to be desired.

Contribution à l'Étude des Syndromes de la Région thalamique. Par PIERRE HILLEMAND. Pp. 182. Paris: Jouve et Cie. 1925. Price, 15 fr.

The chief features of this book are a detailed exposition of the blood-supply of the thalamus, and a careful analysis of the clinical symptoms that result from lesions of the thalamic region.

As it is softenings that most commonly produce the thalamic syndrome it is the distribution of the vessels that determines the form it assumes, for different symptoms are due to involvement of different portions of the thalamus or of neighbouring structures. The author separates out two chief types, the one, due to occlusion of the thalamo-genticulate vessels, is characterized by contractures, disturbances of co-ordination, choreo-athetotic movements, pains and disturbances of sensation, often accompanied by a slight hemiplegia and vasomotor symptoms; in the other, which results from blocking of the retro-mammillary or perforating artery, inco-ordination and an intention-like tremor, sometimes associated with slight sensory changes and choreo-athetotic movements, are the chief symptoms.

There is an interesting discussion on the nature and genesis of the chief symptoms of the syndrome and records of personally observed cases, which add to the value of the book.

L'Odorat. Par H. ZWAARDEMAKER. Pp. 305. Paris: G. Doin. 1925. Price 15 fr.

In this small book Zwaardemaker, to whom we owe most of what we know of the physiology and psychology of the sense of smell, presents in a concise form the results of his own investigations and those of other recent workers on this subject. In addition to chapters on the mechanism of smell and related physiological subjects, he deals with the classification of odours, the chemical constitution of odoriferous substances and their specific energies.

The volume supplies a long felt need in the physiology of the special senses.

Pratique sémiologique des Maladies mentales. Par PAUL SOLLIER, et PAUL COURBON. Paris: Masson et Cie. 1924. Pp. 438, with 89 original drawings.

This book is an excellent guide to the differential diagnosis of abnormal mental states. It is written from the clinical standpoint, and contains very little pathology or psychopathology. The authors do not appear to accept much of the modern teaching resulting from the concept of the unconscious mind.

The preface contains well-deserved complaints concerning the diversity of meanings attached to the large number of technical terms used in psychiatry. The writers remark that the "craze for neologisms has passed from the camp of the patient to that of his physicians." The complaint is a just one, and

some standardization of technical labels is only too necessary to clarify treatises on insanity written in different countries.

The book opens with chapters on the examination of the patient, physical and psychological. They are good, especially where the appearance of the patient is considered. The neurological aspect of the examination is sketchy, and the procedure of lumbar puncture and investigation of the cerebro-spinal fluid does not receive adequate attention.

The authors pass to a detailed consideration of the common symptoms of persons of unsound mind: excitement, depression, ideas of persecution, of grandeur, illusions and hallucinations, the suicidal impulse and the psychoneuroses; they cover this large field adequately and with an interesting style. The chapter on states of depression may be singled out as particularly good. The appearance and complaints of a depressed patient are set out with almost dramatic force; the differential diagnosis of melancholic states, and the disposal and treatment of such cases, can only have been written by medical men of long clinical experience. It is interesting to read that Drs. Sollier and Courbon insist on the importance of removing an acutely depressed person from his home environment.

There is a chapter on the differential diagnosis of general paralysis, which is hardly in agreement with most writers. Drs. Sollier and Courbon do not seem convinced of the reliability of the Wassermann reaction in the cerebro-spinal fluid, and state that it may be negative when general paralysis is definitely established. The cytology of the fluid is barely mentioned, and the colloidal gold tests omitted. There is no discussion on the treatment of paresis by induced hyperpyrexia.

The sections of the book dealing with prognosis and the legal procedures in France are excellent, and the whole book suggests extensive knowledge of clinical work. There are eighty-nine illustrations, many of them crayon drawings, which are a valuable addition to the text. The treatise may be recommended warmly to students of psychiatry. It places the reader before his patient, and teaches how to examine, how to reach a diagnosis, and what measures should be adopted to ensure safety and recovery.

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To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.